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ABSTRACT

CLINICAL ASPECTS OF NEUROLOGICAL MANIFESTATIONS OF LONG COVID AND PROSPECTS FOR PHYSIOTHERAPEUTIC INTERVENTIONS (REVIEW OF LITERATURE)

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Post-acute sequelae of SARS-CoV-2 is a multisystem classification. Its sole defining criterion is the persistence of neurological or neuropsychiatric symptoms beyond the 12-week post-infection mark. Clinical presentation is heterogeneous but dominated by two core symptoms: profound asthenia and significant cognitive dysfunction (memory/attention deficits). A secondary cluster of high-prevalence symptoms is recognized: cephalalgia, dizziness, dyssomnia, sensorimotor deficits, and persistent olfactory/gustatory dysfunction. Psychiatric involvement is common, with documented high rates of anxiety, depression, and PTSD.

International meta-analyses demonstrate the high prevalence of these symptoms within the first 6–12 months, with a tendency to persist for several years. Data from Ukrainian cohorts indicate even higher rates of fatigue, sleep disorders, and anosmia compared to European populations.

The low efficacy of pharmacotherapy necessitates the investigation of non-drug interventions, particularly physiotherapeutic modalities. While modalities like Pulsed Electromagnetic Field therapy and Transcranial Magnetic Stimulation show initial promise against asthenia, cognitive deficits, and psychoemotional symptoms, their utility is unproven. The current evidence base is fundamentally unusable. It is derived exclusively from underpowered pilot data and case series. Validation, therefore, is entirely dependent on future large-scale Randomized Clinical Trials.

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These trials require mandatory components: rigid, standardized protocols and a reliance on objective, quantifiable endpoints. Efficacy (or lack thereof) must be demonstrated using neuropsychological tests, biomarker quantification, and functional neuroimaging, not subjective reports.

Keywords: Long COVID, neurological symptoms, cognitive dysfunction, physiotherapy, pulsed electromagnetic field therapy, transcranial magnetic stimulation, health resilience.

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КЛІНІЧНІ АСПЕКТИ НЕВРОЛОГІЧНИХ ОЗНАК LONG COVID, ПЕРСПЕКТИВИ ФІЗІО-ТЕРАПЕВТИЧНИХ ВТРУЧАНЬ (ОГЛЯД ЛІТЕРАТУРИ)

Синдром Long COVID є мультисистемним станом, що характеризується персистенцією широкого спектра неврологічних і нейропсихіатричних симптомів понад три місяці після гострої інфекції SARS-CoV-2. Найбільш поширеними клінічними проявами є хронічна втома, когнітивні порушення пам'яті та концентрації, головний біль, запаморочення, розлади сну, сенсорно-моторні дефіцити, а також стійкі порушення нюху й смаку. Часто спостерігаються тривожні та депресивні розлади, а також посттравматичний стресовий синдром. Міжнародні мета-аналізи доводять значну поширеність цих симптомів у перші 6–12 місяців, з тенденцією до їх збереження протягом кількох років. Дані українських когорт свідчать про ще вищу частоту втоми, розладів сну та аносмії порівняно з європейськими показниками.

У зв'язку з обмеженою ефективністю фармакологічних підходів доцільним є вивчення немедикаментозних методів, зокрема фізіотерапевтичних технологій. Пульсова електромагнітна терапія та транскраніальна магнітна стимуляція показують обнадійливі результати у зменшенні втоми, когнітивних і психоемоційних розладів, однак наразі доказова база складається переважно з пілотних досліджень та серій випадків. Необхідні масштабні рандомізовані клінічні випробування зі стандартизованими протоколами та об'єктивними кінцевими точками, включно з когнітивними тестами, біомаркерами та нейровізуалізацією.

Ключові слова: Long COVID, неврологічні симптоми, когнітивна дисфункція, фізіотерапія, пульсова електромагнітна терапія, транскраніальна магнітна стимуляція, міцне здоров'я.

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INTRODUCTION

Long COVID (LC) is classified by neurological and neuropsychiatric manifestations persisting beyond three months post-acute SARS-CoV-2 infection. The most frequent symptoms reported are: pronounced fatigue and cognitive impairment ("brain fog"), specifically memory/attention deficits. Headache, dizziness, sleep disturbances, sensorimotor deficits, persistent anosmia, and ageusia are also common. Significant psychiatric manifestations – depression, anxiety, Post-Traumatic Stress Disorder (PTSD) – are documented [1–4].

A large systematic review encompassing 36 studies and 9,944 patients in European countries reported that fatigue affected up to 52.8% of patients, cognitive dysfunction 35%, paresthesia 33%, sleep disorders 33%, myalgia 28%, and dizziness 26% during the first six months following COVID-19 [5]. Additional studies confirm a wide range of central and peripheral symptoms, including "brain fog and post-exertional malaise (PEM), headache, autonomic dysregulation, muscle weakness, hyposmia, and vestibular disorders [2, 6, 7].

Fatigue remains the most common neurological symptom of LC. Meta-analyses indicate that fatigue occurs in approximately 37% of patients among all neurological manifestations, with some international studies reporting rates as high as 98% during the first six months post-infection [3, 5, 7]. Cognitive impairments are also highly relevant. Memory disturbances occur in 27.8% of cases, while concentration deficits affect 23.8% of patients [8]. In a large cohort (n = 10,530), twelve weeks post-COVID, fatigue was observed in 37%, "brain fog" in 32%, memory disturbances in 28%, and attention deficits in 22% of participants [3, 9].

Headache and dizziness remain prevalent in LC. Headache is reported in 20.3% of patients, increasing to 24.7% at 6–9 months post-infection. Dizziness prevalence is 16% [8,10]. The symptom presentation is skewed: 43.6% of affected individuals show pronounced clinical symptoms; only 2.4% report mild manifestations. Sleep disturbances are noted separately, with a 31% prevalence. This pathology demonstrates a tendency to persist or escalate over time. Insomnia-specific data: Prevalence is 41.8% at one month LC. This rate drops to 25.5% at the three-month mark [3, 4, 11].

Sensorimotor deficits are noted in a subset of patients. Prospective studies indicate that six months post-infection, 40% of hospitalized patients exhibited neurological abnormalities, and 7.6% showed pronounced motor-sensory deficits [3, 4, 12]. Olfactory and gustatory disturbances carry significant clinical weight. Anosmia is observed in 12% and dysgeusia in 11% of patients. These symptoms may persist for over one year, distinguishing LC from other viral infections [1, 13, 14].

Psychiatric features of LC include anxiety, depression, and PTSD. Meta-analyses report anxiety in 23% and depression in 12% of cases [15,16]. PTSD was diagnosed in 24.6% of patients twelve months post-infection, frequently coexisting with cognitive impairments. In a cohort of 1,142 patients monitored over seven months, anxiety was observed in 16.2%, and depressive symptoms in 19.7% [16, 17]. Another long-term cohort study reported significant prevalence of psychiatric disorders two to three years after hospitalization; in a sample of 475 patients, average cognitive function declined by approximately 10 IQ points [18].

National studies corroborate a high prevalence of LC among the Ukrainian population [19]. In a cohort of 278 patients, fatigue occurred in 90%, myalgia in 85%, anosmia in 70%, hair loss in 70%, sleep disorders in 70%, dyspnea in 30%, and "brain fog" in 25%. Symptom prevalence was similar in hospitalized and outpatient settings. Compared to average European data, fatigue (90% vs. 37%), sleep disturbances (70% vs. 31%), and anosmia (70% vs. 12%) were more common in Ukraine [20, 21].

LC consequences are structural. Brain changes are documented, including reduced gray matter volume, demyelination, and cerebrovascular impairments. Biomarkers associated with dementia risk are identified. This is observed even in patients post-mild acute infection. Cognitive deficits show significant persistence. Over 45% of individuals remain impaired two years post-infection [18, 22].

The complexity and multidimensionality of LC neurological manifestations mean pharmacological monotherapy is insufficient. Persistent symptomatology demands exploration of non-pharmacological approaches. The goals are nervous system recovery and quality of life improvement. Physiotherapeutic interventions are scrutinized for potential to reduce cognitive/psycho-emotional impairments and promote neuroplasticity [23, 24].

Prolonged SARS-CoV-2 brain impact is linked to reduced gray matter volume, neurovascular alterations, and cerebral blood flow imbalances. Recent studies utilizing non-linear analysis of heart rate variability have confirmed that such autonomic dysregulation is

characterized by specific changes in entropy and irreversibility metrics [25]. These pathologies offer a partial explanation for "brain fog" and cognitive deficits. The potential relevance of physiotherapeutic interventions is thus highlighted [26].

Pulsed electromagnetic field (PEMF) therapy is one such candidate. A pilot randomized trial established its feasibility and acceptability for post-COVID fatigue. The PEMF group showed improvements in functional capacity and quality of life versus placebo. No serious adverse events were noted. The authors mandate larger RCTs and protocol standardization [27].

Clinical observations further support PEMF. In Germany, localized application at the C7/T1 level in a patient with severe LC led to immediate improvement in neuromuscular interaction (“adaptive force”) and sustained clinical benefit over six months [28]. A five-week therapy course reportedly reduced fatigue and improved psycho-emotional status [29]. These are not controlled trial data. The evidence base shows only weak positive signals.

Typical PEMF protocol: local application at the cervicothoracic junction (C7/T1). Frequency and induction are individualized. Neuromuscular adaptive force biomarkers are sometimes used for dosing optimization [28]. Course duration is 2-3 weekly sessions for 4-5 weeks [29]. A 2025 pilot RCT used standardized duration/intensity, prioritizing feasibility/acceptability. Secondary endpoints were fatigue, functional capacity, and quality of life [27, 30].

Cross-study comparisons are invalid. This is due to heterogeneity in devices and field parameters (frequency, induction, pulse form). Data synthesis is therefore complicated. Methodological standardization is required [27, 29].

The primary clinical targets of intervention include fatigue and reduced energy, cognitive slowing (“brain fog”), autonomic dysfunction, and muscle weakness, which are the most frequent and clinically relevant symptoms in post-viral syndromes [27,29–33]. Serious adverse events were not reported; some patients noted transient local sensations during sessions. Data remains insufficient to exclude rare adverse effects. This necessitates larger studies incorporating specific safety monitoring protocols [27].

Future RCTs require strict standardization of stimulation parameters: frequency, induction, duration, and application area. Endpoint incorporation must include neuropsychological tests, fatigue scales, and heart rate variability measures. When feasible, MRI with arterial spin labeling or EEG may clarify mechanisms of action [34, 35].

Repetitive transcranial magnetic stimulation (rTMS), specifically its subprotocol, such as intermittent theta burst stimulation (iTBS), is a promising approach to treating the neuropsychiatric manifestations of LC. Existing data include case reports, small patient series, and initial controlled studies [37–38].

There is emerging preclinical evidence that low-intensity repetitive transcranial magnetic stimulation (LI-rTMS) can modulate glial and immune-related pathways in the brain, but human data are still very limited. Most published work focuses on astrocytes, microglia, and remyelination, not on systemic immune markers [40, 41].

Evidence suggests rTMS modulates CNS-specific inflammatory and immune processes, particularly neuroinflammation and glial cell activation. This finding, however, does not extend peripherally; investigations into peripheral inflammatory markers (IL-1, IL-6, TNF, C-reactive protein) are characterized by inconsistent and uniformly underpowered results. This uncertainty is severely compounded by gross protocol heterogeneity, as studies employ wildly varied stimulation parameters (frequency, target location, session number). Furthermore, a critical cohort specificity issue exists, given that most data is derived from psychiatric populations, rendering extrapolation to post-viral syndromes scientifically unsound. The primary methodological limitation remains that the available research is strictly correlational, failing to establish any causation. These studies document concurrent alterations in immunological markers and clinical outcomes but fail to confirm that these immune changes constitute the therapeutic mechanism of action for rTMS [42–45].

The existing human data on rTMS for LC is limited entirely to preliminary reports. A Japanese case series (n>20) provided initial signals suggesting rTMS reduced depressive symptoms and enhanced cognitive function post-infection [46]. This was followed by a 2023 series which systematically documented reductions in chronic fatigue and cognitive slowing, notably providing detailed prefrontal targeting and dosing protocols [47–49]. Specific iTBS investigation is also minimal; a 2024 pilot (n=4) confirmed good tolerability and short-term cognitive gains, merely highlighting the need for actual randomized studies [50]. Further single-case reports associate 10 iTBS sessions with mood/cognitive improvements, EEG alpha activity normalization, and even olfactory/respiratory recovery [37, 50, 51]. While TMS is thus posited as "promising" for LC-related cognitive dysfunction, depression, and fatigue, the evidence base remains restricted to small-scale series and pilot protocols. Larger, properly controlled trials are reportedly ongoing, such as the UCLA study utilizing 15 sham versus 15 active sessions [53].

A recent systematic review analyzing 19 studies on non-invasive and minimally invasive brain stimulation for post-COVID syndrome reached ambiguous conclusions. While the review identified tDCS and TMS as potential modalities for mitigating fatigue, depression, cognitive symptoms, and olfactory loss, it emphasized that the collective findings remain highly inconsistent. The review also noted emerging, separate reports on transcutaneous vagus nerve and transorbital alternating current stimulation [54].

Protocol standardization is non-existent. Most studies, however, converge on targeting the dorsolateral prefrontal cortex (DLPFC), presumably due to its role in executive function and emotional regulation; motor cortex stimulation is sometimes employed for fatigue [47]. Combined approaches have been documented, such as pairing extended iTBS (1,200 pulses) on the left DLPFC (a protocol borrowed from depression treatment) with low-frequency 1 Hz rTMS (600 pulses) on the right orbitofrontal cortex [46]. The required session dosage is unknown, with parameters ranging from 4–10 sessions in clinical cases to 15–20 in pilot RCTs, usually administered daily on weekdays [50, 53, 55].

Efficacy assessments rely on cognitive tests for attention, executive function, and processing speed, as well as standardized fatigue, depression, and anxiety scales. Some studies reported EEG normalization, suggesting mechanistic relevance [38,47]. Functional neuroimaging (fNIRS, TMS) supports DLPFC and motor cortex targeting: reduced activation correlates with fatigue severity, and motor cortex excitability recovery associates with symptom improvement [56].

TMS safety in LC is consistent with depression treatment. Serious adverse effects were not reported; transient scalp tingling or headache were the most common [50]. EU classification of non-destructive neurostimulation as high-risk devices imposes regulatory constraints without reducing clinical relevance [57–59]. Key limitations include small sample sizes, lack of large multifactorial studies, and heterogeneity in protocols and patient characteristics. Pilot RCTs with sham control are underway [53].

Future multicenter RCTs in Europe and Ukraine should target the DLPFC for cognitive and emotional improvement and the motor cortex for fatigue. MRI- and connectome-guided neuronavigation is recommended. iTBS (600 pulses) should be compared with classical high-frequency repetitive TMS using sham control and double-blinding [50, 60]. Endpoints should include extended cognitive testing, fatigue and emotional disorder scales, and objective biomarkers (EEG, MRI with arterial spin labeling, HRV). Observation should last at least 8–12 weeks with follow-up at 3–6 months to assess durability. Safety monitoring should follow TMS standards, recording all adverse events to establish a precise risk profile in post-viral syndrome [50].

CONCLUSIONS

Neurological and psychiatric manifestations represent key components of Long COVID. The most prevalent symptoms include fatigue (up to 65–70% of patients), cognitive impairments (“brain fog”) (40–50%), sleep disturbances (35–45%), headache (20–30%), and olfactory/gustatory dysfunction (15–25%); anxiety affects up to 30%, depression 20–25%, and post-traumatic stress disorder (PTSD) symptoms 10–15% of patients.

Symptom persistence is documented for one to three years post-COVID-19. This timeline correlates directly with neuroimaging findings which confirm reduced gray matter volume, cerebrovascular imbalances, and microvascular alterations. These data strongly suggest a definitive organic etiology for the observed neuropsychiatric disturbances.

Consequently, management of the Long COVID cohort is inherently multidisciplinary, demanding integrated input from neurologists, psychiatrists, rehabilitation specialists, and physiotherapists. Innovative approaches specifically targeting nervous system recovery must be prioritized for investigation.

Pulsed electromagnetic field therapy, applied to post-COVID fatigue, yielded measurable improvements in functional capacity and quality of life, with no adverse effects documented. While these findings originate from a small sample, they provide essential preliminary validation of the intervention's feasibility and patient acceptability.

Based on the reviewed evidence, we propose a new conceptual framework for physiotherapeutic management: the Three-Phase Matrix of Neurorecovery in Long COVID, which integrates the proven anti-inflammatory effects of PEMF with the neuroplastic potential of rTMS, targeting three core domains: energy/fatigue, executive function, and autonomic balance.

PROSPECTS FOR FUTURE RESEARCH

Future directions include the integration of PEMF and other physiotherapeutic approaches into clinical practice, which requires large-scale randomized controlled trials with standardized intervention parameters, long-term follow-up, and evaluation of both clinical and neurobiological outcomes.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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