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Mini review

Post-COVID-19 Syndrome with Complex Neuropsychiatric Manifestations (CNPM) and Presence of SARS-CoV-2 Spike Protein: A Case Report and Literature Review

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Abstract

Post-COVID-19 syndrome, commonly referred to as long COVID, represents a major clinical challenge characterized by persistent multisystem symptoms following acute SARS-CoV-2 infection. This case report presents a 47-year-old female patient with persistent complex neuropsychiatric manifestations since a probable SARS-CoV-2 infection in February 2020. The clinical presentation combines neurological symptoms (postural vertigo, sensory hypersensitivity), psychiatric manifestations (generalized anxiety, depressive symptoms), and somatic complaints (chronic fatigue, thrombocytosis). We propose an integrated diagnostic and therapeutic approach based on the emerging hypothesis of "Spikeopathy," involving persistence of the SARS-CoV-2 Spike protein and its neuroinflammatory effects. The challenges of multidisciplinary outpatient management are discussed, along with recommendations for optimizing care pathways for these complex patients.

Keywords: Long COVID, Post-COVID-19 syndrome, Neuropsychiatric manifestations, Spike protein, Multidisciplinary approach

Introduction

The COVID-19 pandemic has revealed a complex clinical phenomenon: the persistence of multisystem symptoms in some patients following the acute phase of SARS-CoV-2 infection. This condition, termed post-COVID-19 syndrome or "long COVID," affects approximately 10-30% of infected individuals, regardless of the initial infection's severity [1,2]. The neuropsychiatric manifestations of long COVID are particularly disabling and pose considerable diagnostic and therapeutic challenges to healthcare providers worldwide.

Recent literature suggests the involvement of persistent neuroinflammatory mechanisms, potentially mediated by the SARS-CoV-2 Spike protein [3,4]. This hypothesis, known as "Spikeopathy," proposes that persistence of the Spike protein or viral fragments sustains a chronic inflammatory cascade affecting both the central and peripheral nervous systems [5]. Understanding these mechanisms is crucial for developing effective treatment strategies and improving patient outcomes. This article describes the comprehensive case of a patient presenting with post-COVID-19 syndrome characterized by complex neuropsychiatric manifestations and proposes an integrated diagnostic and therapeutic approach for managing such challenging cases in clinical practice.

Objectives

Main Objective

The primary objective of this study is to contribute to a better understanding of this emerging clinical entity and to promote multidisciplinary management adapted to the biopsychosocial complexity of these syndromes.

Specific Objectives

This case report aims to:

i. Describe the clinical presentation of post-COVID-19 syndrome with predominantly neuropsychiatric manifestations.

ii. Analyze potential pathophysiological mechanisms including the "Spikeopathy" hypothesis.

iii. Propose an integrative diagnostic framework for these complex cases.

iv. Develop an Integrated Psychiatric and Psychotherapeutic Treatment Plan (IPTP).

v. Identify the challenges of multidisciplinary outpatient management.

vi. Formulate evidence-based recommendations to optimize the care pathway for these patients.

Clinical Case Presentation

Patient Demographics and Background

Mrs. Eva (name given to the patient for anonymity purposes) is a 45-year-old secondary school teacher working from 50 to 60 % capacity, married with two teenage children aged 16 and 18 years. She holds a Bachelor's degree and resides in Neuchâtel, Switzerland. The patient has been on sick leave since October 2024 due to the severity and persistence of her symptoms.

Chief Complaint and Presenting Symptoms

The patient presented with a constellation of neuropsychiatric symptoms including persistent dizziness, photophobia, and chronic insomnia that have persisted since February 2020. She reported ongoing fatigue described as both profound physical and mental exhaustion that significantly impairs her daily functioning and professional capabilities.

History of Present Illness

Between 2020 and 2025, the patient experienced persistent, fluctuating symptoms that began with severe rotational vertigo present continuously in all positions. While this symptom partially improved after three years, it persists when standing and significantly impacts her quality of life. Initially, she also suffered from intense muscle weakness that gradually subsided over time but left her with ongoing functional limitations.

During the first year of illness, she reported nocturnal awakenings accompanied by median chest burning and dyspnea, which became less frequent after two years but never completely resolved. Her respiratory difficulties required corticosteroid treatment, and she experienced respiratory crises, particularly during summer months, for approximately six months. These episodes were often triggered by environmental factors and required urgent medical attention.

The patient developed marked hypersensitivity to artificial light and heat that persisted over several years, significantly affecting her ability to work in typical classroom environments. Her sleep disturbances showed a complex pattern of evolution: initially, she had trouble falling asleep (not until after 3 AM) for two years, followed by sleep fragmentation with 3 AM awakenings for approximately one year, and subsequently early awakenings at 4 AM. Light sleep and severe morning fatigue alternated with these patterns for several years, creating a cycle of sleep deprivation and daytime dysfunction.

Additional symptoms included calf cramps and hand tremors under stress and when standing for approximately six months, occasional ophthalmic migraines, possible hypoglycemic episodes, and severe fatigue with dyspnea persisting for more than six months. The clinical picture was further complicated by cognitive fog with concentration and coordination difficulties that fluctuated over three years, significantly impacting her professional performance as an educator.

In the past year, she has suffered from persistent vertigo and insomnia requiring psychiatric care. She initially attempted to resume work at 100% capacity, but following a viral infection (suspected by her general practitioner), she experienced a significant

relapse into exhaustion. Vertigo symptoms returned with intensity when exposed to environments with intense light and sensory stimuli, such as department stores, though her tolerance to artificial lights has shown some improvement. Her insomnia improved temporarily with melatonin (0.5 mg from December to July 2024), and her current emotional state is characterized by sadness linked to functional limitations rather than a primary mood disorder.

Psychiatric and Medical History

Psychiatric History: The patient's personal psychiatric history includes a previous burnout episode that required brief psychological support, mood disorder following two miscarriages (without formal follow-up), and depression in 2020. Her personality profile reveals obsessive-compulsive traits, dependent characteristics, avoidant behaviors, and anxious tendencies. Her family psychiatric history is significant for a sister with autism spectrum disorder complicated by depression, a maternal aunt with schizophrenia, paternal history of depression, and a father with post-stroke depression.

Medical History: Key medical events include a probable (untested) COVID-19 infection in early 2020, confirmed Lyme disease in March 2020 (treated), functional vestibular disorder diagnosed in November 2020, chronic fatigue and tension headaches, and thrombocytosis detected in June 2024.

Clinical Evolution Timeline: The patient's clinical course from 2020 to 2025 demonstrates the chronic and fluctuating nature of her condition:

i. 2020: Fully incapacitated for work from February to June, underwent ENT and vestibular evaluations, experienced fluctuating work capacity.

ii. 2021-2022: Persistent dizziness and chronic fatigue, requiring neurological and psychological consultations.

iii. 2023: Period of total work incapacity and initiation of vestibular rehabilitation.

iv. 2024: Temporary return to full work capacity from January to May, followed by a relapse with new vertigo episodes and persistent fatigue.

v. 2025: Partial improvement, begun receiving disability benefits, undergoing gradual work reintegration.

Current Clinical Status

Neurological Manifestations: The patient currently experiences persistent rocking vertigo with episodic crises, marked hypersensitivity to light and noise, and bifrontal headaches occurring approximately 10 days per month.

Psychiatric Symptoms: Her psychiatric presentation includes generalized anxiety (Hamilton Anxiety Scale score 21/30), reactive sadness (Beck Depression Inventory score 7/10), ongoing sleep disturbances, and irritability that affects her interpersonal relationships.

Somatic Complaints: She reports severe fatigue (rated 8/10), significant concentration difficulties (rated 9/10), persistent thrombocytosis, and nocturnal sweating that disrupts her sleep quality.

Functional Impact: The cumulative effect of these symptoms has resulted in complete work incapacity and significant restrictions in social, leisure, domestic, and family life activities.

Results: Multiaxial Diagnosis and Pathophysiological Integration

Comprehensive Diagnostic Formulation

Primary Psychiatric Diagnoses (ICD-10/DSM-5):

The patient meets criteria for:

i. F41.1 Generalized Anxiety Disorder (Hamilton Anxiety Scale 21/30).

ii. F33.0 Recurrent Depressive Disorder with current mild episode (Beck Depression Inventory 7/10).

iii. F48.0 Neurasthenia/Chronic Fatigue Syndrome.

iv. F45.8 Other Somatoform Disorders classified as post-viral functional somatic syndrome.

Somatic Diagnoses:

Her medical conditions include:

i. U09.9 post-COVID-19 condition (unspecified)

ii. H81.8 Persistent Perceptual Postural Dizziness (PPPD)

iii. D75.1 Secondary thrombocytosis

iv. A69.2 Lyme disease (history, treated)

v. G44.2 Chronic tension-type headaches

Psychosocial and Environmental Factors

Significant stressors include fluctuating work capacity with return-to-work pressures, a fragmented diagnostic pathway requiring multiple consultations, and shifts in parental and marital roles due to her functional limitations.

Personality Profile

Her personality characteristics include obsessive-compulsive traits (perfectionism, control needs), dependent features (need for reassurance, difficulty making decisions), avoidant behaviors (fear of judgment, hypersensitivity), and anxious tendencies (negative anticipation, rumination).

Integrated Clinical Understanding

This case presents a complex post-COVID-19 syndrome with neuropsychiatric predominance, consistent with the emerging concept of "Spikeopathy." The neurological components include postural dizziness, sensory hypersensitivity, and chronic fatigue, possibly linked to neuroinflammation from persistent Spike protein [6].

The psychiatric manifestations consist of severe anxiety and mild depressive symptoms that interact bidirectionally with neurological symptoms, where anxiety amplifies vertigo perception through somatic hypervigilance, and functional limitations drive reactive depression. Pre-existing vulnerabilities including obsessive and anxious personality traits, past mood disorders, and burnout history [7] have likely contributed to symptom severity and chronicity. Maintaining factors include a vicious cycle of physical symptoms, anticipatory anxiety, and avoidance behaviours [8], while contextual factors encompass the complex diagnostic journey, lack of medical recognition, and socio-professional stressors.

Pathophysiological Mechanisms

The pathophysiology of this patient's post-COVID-19 syndrome likely involves multiple interconnected mechanisms. The "Spikeopathy" hypothesis suggests that persistence of SARS-CoV-2 Spike protein fragments may maintain chronic inflammation even in the absence of active viral replication, leading to sustained immune dysregulation and neuroinflammatory processes (Figure 1).

Figure 1: Pathophysiological Mechanisms of Long Covid Syndrome Schema.

Integrated Psychiatric and Psychotherapeutic Treatment Plan (IPTP)

Pharmacological Interventions

The current pharmacological approach includes:

i. Vortioxetine (Brintellix) with reassessment planned at 8 weeks.

ii. Melatonin 0.5 mg for sleep regulation.

iii. Aspirin Cardio 100 mg for thrombocytosis management.

1. Proposed additional medications include:

i. Buspirone 5-10 mg twice daily for generalized anxiety [9].

ii. Pregabalin titrated to 75-150 mg/day for anxiolytic and neurological modulation [10].

iii. Low-dose Amitriptyline 10-25 mg in the evening for tension headaches and sleep improvement [11].

iv. Monthly evaluation of treatment efficacy and side effects is planned, along with regular hematology monitoring for thrombocytosis.

Psychotherapeutic Interventions

Cognitive Behavioral Therapy (CBT):

Weekly sessions of 45-60 minutes focus on:

i. Psychoeducation about post-COVID syndrome and mind-body interactions.

ii. Reducing avoidance and hypervigilance behaviors.

iii. Cognitive restructuring of catastrophic thoughts.

iv. Gradual exposure to anxiety-provoking situations.

v. Comprehensive stress management techniques [12].

Acceptance and Commitment Therapy (ACT):

Integrated within CBT sessions, ACT focuses on:

i. Acceptance of persistent symptoms.

ii. Clarification of personal values despite functional limitations.

iii. Development of psychological flexibility.

iv. Mindfulness approaches for somatic symptom management [13].

Mindfulness-Based Cognitive Therapy (MBCT):

An 8-session group or individual program targeting:

i. Non-judgmental awareness of body sensations.

ii. Reduced emotional reactivity.

iii. Adapted meditation techniques suitable for patients with dizziness [14].

Mind-Body and Rehabilitation Interventions

Biofeedback and Relaxation:

i. Heart rate variability biofeedback for autonomic regulation and EMG biofeedback for muscle relaxation [15].

ii. Progressive muscle relaxation (Jacobson technique).

iii. Diaphragmatic breathing exercises.

iv. Autogenic training [16].

Physical Activity and Cognitive Rehabilitation

i. Graded exercise therapy adapted to individual tolerance including walking and swimming [17].

ii. Energy management and pacing techniques [18].

iii. Attention and concentration exercises.

iv. Compensatory cognitive strategies.

v. Structured routines to reduce cognitive load [19].

Multidisciplinary Care Coordination

The treatment team includes:

i. Psychiatrist for care coordination and pharmacotherapy.

ii. Psychologist for psychotherapy delivery.

iii. Neurologist with vestibular expertise.

iv. Internal medicine/immunology specialist for long COVID follow-up.

v. Vestibular physiotherapist.

vi. Occupational therapist for work adaptation [20].

Care coordination procedures involve quarterly multidisciplinary reviews, maintenance of a shared treatment plan and medical file, and regular written communications between team members [21].

Psychosocial Support Systems

Socio-professional Support:

Successful mediation with the Employer and the Swiss Federal Office for Disability Insurance (DI)has resulted in:

i. 80% salary coverage by DI.

ii. Adjusted workload to 12 periods (approximately 46% capacity).

iii. Planned gradual return to work program [22] based on the progress of recovery under the IPTP plan.

Family Support:

i. Psychoeducation for spouse and family members.

ii. Appropriate expectation setting.

iii. Strategies to avoid codependency patterns [23].

iv. Community Resources.

v. Connection with long COVID patient associations.

vi. Participation in online support groups [24].

Discussion

Pathophysiological Mechanisms of Post-COVID-19 Syndrome

The pathophysiology of post-COVID-19 syndrome remains partially elucidated, with several complementary hypotheses emerging from recent research. The “Spikeopathy” hypothesis suggests that persistence of SARS-CoV-2 Spike protein in the body may maintain chronic inflammation, even in the absence of active viral replication [25]. *Patterson, et al.* demonstrated the presence of Spike protein fragments in monocytes up to 15 months post-infection [26], which may lead to sustained immune dysregulation and ongoing symptomatology.

Neurologically, several mechanisms could contribute to the observed clinical picture:

i. Autonomic dysfunction may result from Spike protein alteration of ACE2-expressing autonomic structures, causing dysautonomia [27].

ii. Persistent neuroinflammation is evidenced by elevated cerebrospinal fluid inflammatory markers in long COVID patients with neurological symptoms [28].

iii. Cerebral microangiopathy may develop through microvascular alterations linked to Spike-induced endothelial injury [29].

iv. Microglial activation leads to sustained neuroinflammation and altered neural homeostasis, contributing to cognitive and emotional symptoms [30].

The patient's thrombocytosis may also reflect systemic inflammation [31] and could potentially serve as a useful biomarker for monitoring disease activity.

Somato-Psychiatric Interplay in Long COVID

This case effectively illustrates the complex interaction between somatic and psychiatric factors in long COVID syndrome. Neuroinflammation can directly induce psychiatric symptoms through multiple pathways: systemic inflammation alters mood and anxiety circuits [32], and the Spike protein may disrupt serotonergic signaling via ACE2 interactions [33].

Additionally, the subjective experience of chronic illness amplifies psychological distress through several mechanisms:

i. Symptom unpredictability creates a sense of insecurity and loss of control [34].

ii. Lack of social and medical recognition increases feelings of invalidation [35].

iii. Functional limitations profoundly affect personal identity and self-concept [36].

iv. Invisible symptoms complicate disability recognition and social understanding [37].

Pre-existing personality traits, particularly perfectionism and anxiety, may increase vulnerability to developing chronic post-viral syndromes [38]. The maintenance of symptoms often involves avoidance behaviors and somatic hypervigilance that fit well within the cognitive-behavioral model of functional somatic symptom perpetuation [39].

Diagnostic and Therapeutic Challenges

Diagnosing post-COVID-19 syndrome with neuropsychiatric manifestations presents numerous challenges to clinicians:

i. Currently, no pathognomonic biomarker exists [40].

ii. Significant symptoms overlap with other conditions including ME/CFS, fibromyalgia, and somatoform disorders [41].

iii. Risk of both over-diagnosis and under-diagnosis due to increased media attention and variable clinical suspicion among healthcare providers [42].

iv. Marked clinical heterogeneity observed across patients [43].

An integrated diagnostic approach is essential and should include:

i. Detailed infection and symptom chronology.

ii. Exhaustive clinical assessment across multiple domains.

iii. Judicious exclusion of alternative etiologies.

iv. Comprehensive multidimensional biopsychosocial formulation [44].

Therapeutic challenges in outpatient management include:

Resource limitations:

i. Lack of reimbursement for care coordination.

ii. Time constraints.

iii. Limited access to specialized therapies [45].

Institutional barriers:

i. Insufficient collaboration between community and hospital-based care.

ii. Lack of specialized treatment units.

iii. Prolonged waiting times [46].

Administrative burden:

i. Excessive reporting to insurance companies.

ii. Justification of work incapacity.

iii. Heavy documentation requirements [47].

These factors can hinder optimal implementation of integrated treatment plans.

Prognostic Considerations

Longitudinal studies suggest that approximately 70-85% of patients show improvement over 1-2 years, but 15-30% remain symptomatic long-term [48].

Favorable prognostic factors include:

i. Early multidisciplinary care.

ii. Absence of major psychiatric comorbidities.

iii. Good social support systems.

iv. Flexible expectations regarding recovery [49].

Unfavorable prognostic factors include:

i. Severe initial symptoms.

ii. Marked dysautonomia.

iii. Delays in diagnosis and management initiation.

iv. Catastrophizing thought patterns.

v. Persistent avoidance behaviors [50].

In this case, several risk factors for chronicity exist, including symptom severity, delayed diagnosis, and personality vulnerabilities. However, the patient's strong treatment motivation and good insight into her condition serve as positive prognostic indicators that may facilitate recovery.

Recommendations

Clinical Practice Guidelines

Diagnostic Strategy:

i. Implement structured diagnostic approaches using positive diagnostic criteria established by WHO and NICE guidelines [51].

ii. Conduct comprehensive neurological, psychiatric, and somatic assessments.

iii. Systematically search for inflammatory biomarkers, autoimmunity markers, and dysautonomia indicators [52].

iv. Perform neuropsychological evaluation when cognitive deficits are clinically significant.

Care Organization:

Designate a coordinating physician to oversee the multidisciplinary team [53].

Develop written individualized care plans.

Schedule multidisciplinary reassessments every 3-6 months.

Establish specialized care networks for long COVID patients [54].

Therapeutic Approach:

i. Adopt an integrated biopsychosocial model.

ii. Target identified pathophysiological mechanisms including inflammation, dysautonomia, and mitochondrial dysfunction.

iii. Implement gradual adaptation of interventions based on patient response.

iv. Consider emerging therapies such as immunomodulators and anticoagulants on an individual basis [55].

Communication and Therapeutic Alliance:

i. Validate patient experiences and avoid dismissive attitudes.

ii. Eschew simplistic biological versus psychological dichotomies.

iii. Provide transparent information about current scientific understanding.

iv. Actively involve patients in treatment decisions [56].

Research Priorities

Pathophysiology Research:

i. Further investigation of "Spikeopathy" mechanisms.

ii. Comprehensive immunoinflammatory profiling of patients.

iii. Advanced neuroimaging and cerebrospinal fluid studies [57].

Therapeutic Studies:

i. Controlled trials of antiviral agents and anti-Spike monoclonal antibodies.

ii. Investigation of immunomodulators for neuropsychiatric manifestations.

iii. Studies of combined pharmacological and non-pharmacological approaches [58].

Prognostic Research:

i. Identification of reliable predictors of chronicity.

ii. Development of standardized multidimensional assessment tools.

iii. Longitudinal cohort follow-up studies [59].

Health Services Research:

i. Evaluation of different care delivery models.

ii. Comprehensive medico-economic impact studies.

iii. Development of quality indicators for long COVID care [60].

Health Policy Recommendations

Recognition and Support:

i. Develop standardized disability assessment criteria for long COVID.

ii. Establish formal recognition of long COVID as a long-term condition.

iii. Create specific vocational rehabilitation programs [61].

Care Organization:

i. Create designated reference centers for long COVID.

ii. Provide funding for care coordination activities.

iii. Implement ongoing training programs for healthcare professionals [62].

Patient Education and Support:

i. Develop standardized therapeutic education programs.

ii. Provide financial and organizational support for patient associations.

iii. Create validated public information resources [63].

Governance and Funding:

i. Allocate dedicated research resources for long COVID studies.

ii. Fund integrated care pilot programs.

iii. Conduct comprehensive assessments of economic and societal impact [64-67].

Conclusion

This comprehensive case report illustrates the complex neuropsychiatric manifestations of post-COVID-19 syndrome and the substantial challenges they pose to modern healthcare systems. The patient's presentation of persistent postural vertigo, sensory hypersensitivity, generalized anxiety, depressive symptoms, and disabling fatigue exemplifies the multifaceted nature of this emerging clinical entity.

The "Spikeopathy" hypothesis provides a valuable conceptual framework for understanding the intertwined neurobiological and psychological processes underlying this syndrome. Our proposed integrated multidisciplinary approach, based on solid biopsychosocial principles, combines evidence-based pharmacotherapy, structured psychotherapy (including CBT, ACT, and MBCT), mind-body interventions, and comprehensive functional rehabilitation.

However, optimal implementation of such comprehensive care faces significant systemic barriers, including fragmented healthcare delivery, resource limitations, institutional constraints, and excessive administrative burden. Healthcare systems must undergo substantial adaptation to adequately address the specific and complex needs of long COVID patients.

This case also highlights broader fundamental questions regarding the intricate interactions between neuroinflammation and psychopathology, emphasizing the urgent need for targeted therapeutic interventions and innovative organizational approaches. Post-COVID-19 syndrome with neuropsychiatric features represents both a major clinical challenge and an unprecedented opportunity to deepen our understanding of neuro-immuno-psychiatric conditions and their management.

Ultimately, the successful management of these complex patients requires a paradigm shift toward truly integrated, patient-centered care that recognizes the biological reality of post-viral syndromes while addressing their profound psychological and social impacts. Only through such comprehensive approaches can we hope to improve outcomes for the millions of individuals worldwide affected by long COVID.

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Conflict of Interest

None.

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