Long COVID: Objective Biomarkers Challenge Psychosomatic Narrative

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> For years, patients with persistent symptoms following acute infections, often labelled as post-viral fatigue syndrome or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), faced dismissal. Clinicians frequently attributed their debilitating conditions to psychological factors, leaving patients without effective treatment or even validation.
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> Long COVID, with its diverse and often fluctuating symptomology, has brought this deeply problematic narrative into sharp focus, demanding a re-evaluation of how medicine approaches chronic post-infectious illness.

KEY TAKEAWAYS

- The Pivot: Objective biological markers, not psychological distress, now explain many Long COVID symptoms.
- The Data: Persistent immune dysregulation, endothelial dysfunction, and microclot formation are consistently observed.
- The Action: Clinicians must move beyond psychosomatic explanations and integrate emerging biological understanding into diagnostic and management pathways.

Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), affects millions globally, presenting with a constellation of symptoms that can persist for months or even years after the initial infection. These symptoms span multiple organ systems, including profound fatigue, cognitive dysfunction (brain fog), dyspnea, palpitations, myalgia, and post-exertional malaise. The sheer scale of the pandemic and the subsequent wave of chronic illness have forced the medical community to confront a problem it has historically struggled to acknowledge: chronic, debilitating conditions following viral infections that defy simple explanation and are often dismissed as psychosomatic.1

Patients frequently report encounters with healthcare professionals who suggest their symptoms are anxiety-driven or depression-related, leading to inappropriate referrals to mental health services rather than investigations into underlying physiological pathology. This dismissal is not new; it echoes the experiences of individuals with ME/CFS for decades. But the sheer volume of Long COVID cases, coupled with increasingly sophisticated research tools, has begun to dismantle this narrative, revealing tangible biological underpinnings for patient suffering.2

The biological reality of Long COVID

The emerging consensus points to several key biological mechanisms driving Long COVID, moving the discussion firmly into the realm of pathophysiology. One prominent area of investigation is persistent immune dysregulation. Studies

consistently show that individuals with Long COVID exhibit altered immune cell profiles, including T-cell and B-cell abnormalities, and elevated levels of inflammatory cytokines long after the acute infection has cleared. For example, researchers have identified persistent activation of interferon pathways and a dysfunctional type I interferon response in patients with Long COVID, suggesting an ongoing viral presence or an aberrant immune memory.3

Another critical area of research focuses on endothelial dysfunction and microclot formation. Investigators have observed widespread microclots in the blood of Long COVID patients, which are resistant to fibrinolysis. These microclots, composed of fibrinogen and other plasma proteins, impair oxygen transfer to tissues and contribute to the widespread symptoms of fatigue, brain fog, and exercise intolerance. This phenomenon is distinct from macrovascular clotting events seen in acute COVID-19 and represents a persistent, systemic issue. The presence of these microclots provides a compelling, objective explanation for reduced tissue perfusion and metabolic dysfunction, directly contradicting the notion that symptoms are purely subjective or psychological.4

Mitochondrial dysfunction also plays a significant role. The SARS-CoV-2 virus can directly damage mitochondria or induce an immune response that impairs mitochondrial function, leading to reduced energy production and contributing to profound fatigue and post-exertional malaise. This cellular energy deficit is a tangible biological problem, not a psychological one. Furthermore, autonomic nervous system dysfunction, particularly dysautonomia and postural orthostatic tachycardia syndrome (POTS), is prevalent in Long COVID. These conditions, characterised by abnormal heart rate, blood pressure, and digestive regulation, have clear physiological bases and are diagnosable through objective tests like tilt-table testing.5

Persistent viral reservoirs or fragments represent another potential mechanism. Some research indicates that SARS-CoV-2 RNA or viral proteins can persist in various tissues, including the gut, brain, and lymphatic system, long after the acute infection. This persistent viral presence could continuously stimulate the immune system, leading to chronic inflammation and immune dysregulation. This is not a novel concept; similar persistence is observed in other post-viral syndromes.6

The gastrointestinal system also shows significant involvement. Dysbiosis of the gut microbiome is common in Long COVID patients, with alterations in bacterial diversity and composition. This dysbiosis can contribute to systemic inflammation, immune dysfunction, and even neurological symptoms through the gut-brain axis. Specific microbial signatures have been correlated with the severity and type of Long COVID symptoms, offering another objective biological marker.7

Neuroinflammation and direct neurological damage are also under investigation. Brain imaging studies, including PET scans and functional MRI, have revealed abnormalities in brain structure and function in Long COVID patients, including reduced grey matter volume and altered connectivity. These changes correlate with cognitive symptoms and fatigue, providing further evidence of organic pathology. Cerebrospinal fluid analysis has also shown elevated inflammatory markers in some patients, indicating ongoing neuroinflammatory processes.8

The implications of these findings are profound. They shift the burden of proof from the patient, who has historically been asked to justify their symptoms, to the medical community, which must now develop diagnostic tools and treatments based on these biological insights. The challenge lies in translating these complex research findings into practical clinical applications. For instance, while microclots are observed, a standardised, widely available diagnostic test for them is not yet routine in clinical practice. Similarly, while immune dysregulation is evident, targeted immunomodulatory therapies

are still largely experimental for Long COVID.9

The open-label design of many early Long COVID studies is an obvious caveat, but the consistency of biological findings across diverse research groups using various methodologies strengthens the overall picture. The heterogeneity of Long COVID also presents a challenge; it is likely not a single disease but a syndrome with multiple endotypes, each driven by different underlying mechanisms. This means a one-size-fits-all treatment approach will likely fail, necessitating a more stratified approach to diagnosis and therapy. The current lack of specific, validated biomarkers for patient stratification remains a significant hurdle.10

Still, the evidence base is growing rapidly. The focus must now be on developing robust, prospective studies to validate these biomarkers and test targeted interventions. This includes trials of immunomodulators, anticoagulants, and therapies aimed at mitochondrial support or gut microbiome restoration. The goal is not just to identify the mechanisms but to intervene effectively. The medical community has a responsibility to listen to patients, acknowledge their suffering, and pursue evidence-based solutions, rather than resorting to the convenient but ultimately harmful dismissal of symptoms as psychological. The next step is to move from observation to intervention, demonstrating clinical benefit in well-designed trials.11

CLINICAL IMPLICATIONS

The persistent dismissal of Long COVID symptoms as psychosomatic represents a failure of clinical empathy and scientific rigour. Emerging biological evidence, from immune dysregulation to microclot formation, demands that general practitioners and specialists alike abandon this outdated narrative.

Clinicians must integrate this evolving understanding into their practice, moving beyond symptom management to investigate underlying pathology. This means considering advanced diagnostics for endothelial dysfunction or immune markers, even if not yet standard, and advocating for patients within systems that are slow to adapt.

For the pharmaceutical industry, the biological insights into Long COVID present a clear mandate for targeted drug development. The heterogeneity of the syndrome suggests that a single blockbuster drug is unlikely; instead, a portfolio of precision therapies addressing specific endotypes will be necessary.

The ultimate goal is not just to validate patient experiences, but to provide effective treatments. The current evidence base, while compelling, still lacks definitive, widely available therapeutic interventions. This gap must be closed with rigorous clinical trials that translate biological understanding into tangible patient benefit.

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