LONG COVID & PCVS | NEUROLOGICAL SYMPTOMS

Diagnostic Protocol for Long COVID Patients with Neurological Manifestations

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Sequential Cascade Diagnostic Approach

This protocol follows the pathogenic cascade identified in Long COVID neurological manifestations for symptoms such as chronic fatigue, cognitive difficulties or brain fog, microsmia, headache, anxiety providing specific diagnostic tests for each pathophysiological step to enable precise diagnosis and monitoring.

This document is divided into following sections:

a. Methodology for the development of tiered Long Covid neurological diagnostic protocol
b. Tiered model of Long COVID diagnostic tests.

Methodology for the Development of a Tiered Long COVID Neurological Diagnostic Protocol

INTRODUCTION

The development of a comprehensive diagnostic protocol for Long COVID neurological manifestations requires a systematic approach that balances clinical utility, diagnostic accuracy, invasiveness and resource optimization. This methodology section outlines the evidence-based framework employed to create a three-tiered diagnostic protocol specifically targeting neurological sequelae of post-acute COVID-19 syndrome or Long COVID 19. The protocol development process integrated pathophysiological understanding, biomarker studies, and practical clinical considerations to establish a structured diagnostic protocol.

LITERATURE REVIEW AND EVIDENCE SYNTHESIS

Systematic Literature Search

A comprehensive literature review was conducted utilizing multiple biomedical databases including PubMed, MEDLINE, Cochrane Library, and relevant preprint servers. Search parameters encompassed publications from January 2020 to present, focusing on terms including "Long COVID," "post-acute sequelae of SARS-CoV-2 infection (PASC)," "neurological biomarkers," "neurological imaging," "blood-brain barrier dysfunction," and "cognitive impairment post-COVID." Inclusion criteria included peer-reviewed and pre-print studies reporting neurological biomarker elevations in Long COVID patients, validated cognitive assessment tools, and neuroimaging findings correlating with symptom severity.

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Pathogenesis-Based Framework

The protocol structure was fundamentally informed by current understanding of Long COVID neurological pathogenesis. Key pathophysiological mechanisms identified included persistent neuroinflammation, blood-brain barrier disruption, endothelial dysfunction, microglial activation, and potential viral persistence. Each identified mechanism was mapped to corresponding diagnostic test and assessment tools, ensuring comprehensive coverage of potential pathological processes. This pathogenesis-driven approach facilitated the selection of diagnostic tests with mechanistic relevance rather than purely empirical associations.

Biomarker Selection and Classification

Initial Biomarker Compilation

All neurological diagnostic tests demonstrating significant elevation in Long COVID cohorts were systematically compiled from the literature. Each biomarker was evaluated based on multiple criteria correlating with multiple studies and also the pathogenic framework, and correlation with clinical severity scores. The initial compilation yielded over multiple potential diagnostic tests, necessitating a rigorous selection process.

Multi-Criteria Classification System

A comprehensive classification matrix was developed incorporating four dimensions such as cost of the diagnostic tests, clinical utility, type of sample needed (invasive or non-invasive) and availability of tests at various laboratories.

Tiered Protocol Architecture

Tier Stratification Principles

The three-tiered structure was designed following a progressive diagnostic approach, moving from broad screening to specialized assessment. Tier 1 encompasses high-sensitivity screening tools suitable for primary care settings, emphasizing accessibility and cost-effectiveness. Tier 2 introduces system-specific evaluations requiring specialized expertise but remaining within standard hospital capabilities. Tier 3 reserves advanced neuroimaging and invasive procedures for complex cases requiring tertiary care resources.

Progression Criteria Development

Clear progression criteria between tiers were established based on objective thresholds. These criteria incorporated symptom duration (>12 weeks post-acute infection), diagnostic test elevation patterns (particularly the combination of CRP, D-dimer, and/or von Willebrand factor), cognitive assessment scores (Montreal Cognitive Assessment), and functional impairment measures (abnormal six-minute walk test). The progression algorithm ensures efficient resource utilization while maintaining diagnostic sensitivity.

Integration of Functional Assessments

Beyond biomarker evaluation, the protocol incorporates validated functional assessments at each tier. Primary screening includes basic cognitive screening and orthostatic vital signs. Tier 2 expands to comprehensive neuropsychological batteries including Trail Making Test B-A, Digit Span Backward, and Rey-Osterrieth Complex Figure Test. These functional measures provide correlation with biomarker findings and establish baseline measurements for monitoring therapeutic response.

Future Directions and Protocol Evolution

The methodology incorporates provisions for protocol adaptation as emerging evidence refines our understanding of Long COVID neurobiology and also other bio-system diagnostic tests. The protocol architecture facilitates modular updates without requiring complete restructuring, ensuring sustained clinical relevance.

This methodology represents a systematic, evidence-based approach to developing a practical diagnostic protocol for Long COVID neurological manifestations. By integrating pathophysiological understanding with clinical pragmatism, the tiered structure provides a scalable framework adaptable to varying resource environments. As our understanding of Long COVID evolves, this methodological foundation will support continued protocol refinement and optimization.

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Tiered Model of Long COVID Diagnostic Protocol

Primary Screening (Tier 1)
CBC
ESR
C-Reactive Protein [29]
D-Dimer [12,13,14]
Fibrinogen [14,15]
Von-Willebrand Factor [10,11]
Montreal Cognitive Assessment (MoCA) [23,25]
Vital sign assessment [16]
Six minute walk test [27,28]
IL-6 (If affordable) [21]
Electrolyte panel
Thyroid Function (TSH, FT4)
Vitamin B12/D/Folate
Ferritin

Neurological system evaluation (Tier 2)	
BBB Integrity Panel	GFAP (Glial Fibrillary Acidic Protein) [1,2]
	Matrix Metalloproteinase -9 [3,4,5]
	IL-1Beta [6]
	TGF- Beta [1]
	IL-8 [1]
Neuronal damage assessment	S100- Beta [1]
	Neurofilament Light chain (NfL) [8,9]
Comprehensive Cognitive testing	Digit Span Backward [17,24]
	Trail Making Test (B-A score) [24]
	Rey-Ostrich Complex Figure Test [17,24]
	Frontal Assessment Battery [17]
	Stroop Task [17]
Neurophysiological assessment	Functional Near-Infrared Spectroscopy [18,26]
	Sniffin's Stick Test [26]

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Advanced Neuroimaging (Tier 3)	
Specialized Neuroimaging	Dynamic Contrast Enhanced MRI [1]
	PET imaging [19]
	Functional MRI [20]
	3T MRI with DTI [17,22]
CSF analysis	Albumin/CSF ratio [7]
	CSF Cytokines (IL-6, IL-8, TNF-α)
	CSF Neurofilament Light (NfL) [7,8,9]

Reasoning for each test document

Detailed MindMap

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