

Associations Between Peripheral Inflammatory Mediators And Cognitive Performance In Patients With Long COVID

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Long COVID patients showed domain-specific cognitive impairment and reduced TNF, IL-18 and IL-10 plasma levels. Lower IL-4, IL-6, IL-10 and TNF levels, and higher IL-18 levels, were associated with better cognitive performance across specific neuropsychological domains.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																																																								
Long COVID (LC) is characterized by symptoms persisting for at least three months following SARS-CoV-2 infection. Cognitive deficits have been widely reported, along with immune alterations. However, investigations examining potential inflammatory biomarkers of post-COVID cognitive impairment remain scarce. In this study, we investigated the plasma levels of cytokines and their association with cognitive performance in LC.	<table><tr><th></th><th>Controls (n=24)</th><th>Long COVID (n=22)</th><th>p</th></tr><tr><td>Sex (women) n (%)</td><td>22 (91.67)</td><td>19 (86.36)</td><td>0.6589</td></tr><tr><td>Age (years)</td><td>41 (19-52)</td><td>34 (20-59)</td><td>0.0891</td></tr><tr><td>Education (years)</td><td>15 (11-21)</td><td>20.50 (13-28)</td><td>0.0003</td></tr><tr><td>Post-infection interval (months)</td><td>-</td><td>7 (5-13)</td><td>-</td></tr></table> We included 22 individuals with LC-related cognitive impairment and 24 age- and sex-matched healthy controls. Neuropsychological assessment of LC patients was conducted using the Mini-Mental State Examination (MMSE), Functional Independence Measure (FIM), Trail Making Test (TMT), Hopkins Verbal Learning Test-Revised (HVLT), Stroop (STP), Digit Span (DS), Semantic Verbal Fluency (SVF), Symbol Digit Modalities Test (SDMT), Boston Naming Test (BNT), and Proverbs (PVB). Plasma levels of the interleukins IL-4, IL-6, IL-10, IL-1β, IL-18, and Tumor Necrosis Factor (TNF) were quantified using an Enzyme-Linked Immunosorbent Assay (ELISA).		Controls (n=24)	Long COVID (n=22)	p	Sex (women) n (%)	22 (91.67)	19 (86.36)	0.6589	Age (years)	41 (19-52)	34 (20-59)	0.0891	Education (years)	15 (11-21)	20.50 (13-28)	0.0003	Post-infection interval (months)	-	7 (5-13)	-	LC participants showed poorer performance in episodic memory, attention/processing speed, and executive functions, while language, working memory, reasoning, global cognition, and functionality were preserved. TNF, IL-18, and IL-10 plasma levels were significantly lower in LC than in controls, while IL-4 and IL-6 did not differ between groups, and IL-1β was undetectable by ELISA. Lower levels of IL-4, IL-6, IL-10, and TNF were associated with better performance in global cognition, working memory, processing speed, reasoning, verbal fluency, and naming. In contrast, higher IL-18 levels were associated with better semantic verbal fluency. ROC analyses showed excellent diagnostic accuracy for IL-18 and good diagnostic performance for IL-10 and TNF. A TNF (pg/mL of plasma) 0.0002 B IL-18 (pg/mL of plasma) 0.0001 C IL-6 (pg/mL of plasma) 0.0576 D IL-4 (pg/mL of plasma) 0.1666 E IL-10 (pg/mL of plasma) 0.0004 <table><tr><th>Cytokine</th><th>Test</th><th>β (95% CI)</th><th>p</th></tr><tr><td rowspan="2">IL-4</td><td>BNT</td><td>-6.298 (-12.16; -0.4389)</td><td>0.0368</td></tr><tr><td>HVLT</td><td>-2.334 (-4.370; -0.2976)</td><td>0.0274</td></tr><tr><td>IL-6</td><td>DS</td><td>-2.962 (-5.413; -0.5111)</td><td>0.0204</td></tr><tr><td rowspan="4">IL-10</td><td>MMSE</td><td>-12.42 (-22.90; -1.953)</td><td>0.0230</td></tr><tr><td>SDMT</td><td>-7.539 (-14.16; -0.9166)</td><td>0.0283</td></tr><tr><td>PVB</td><td>-39.76 (-78.02; -1.496)</td><td>0.0426</td></tr><tr><td>HVLT</td><td>-9.875 (-18.81; -0.9417)</td><td>0.0324</td></tr><tr><td>IL-18</td><td>SVF</td><td>10.90 (0.4188; 21.38)</td><td>0.0424</td></tr><tr><td>TNF</td><td>BNT</td><td>-25.22 (-49.35; -1.095)</td><td>0.0415</td></tr></table>	Cytokine	Test	β (95% CI)	p	IL-4	BNT	-6.298 (-12.16; -0.4389)	0.0368	HVLT	-2.334 (-4.370; -0.2976)	0.0274	IL-6	DS	-2.962 (-5.413; -0.5111)	0.0204	IL-10	MMSE	-12.42 (-22.90; -1.953)	0.0230	SDMT	-7.539 (-14.16; -0.9166)	0.0283	PVB	-39.76 (-78.02; -1.496)	0.0426	HVLT	-9.875 (-18.81; -0.9417)	0.0324	IL-18	SVF	10.90 (0.4188; 21.38)	0.0424	TNF	BNT	-25.22 (-49.35; -1.095)	0.0415	LC patients exhibited domain-specific cognitive impairment and reduced levels of inflammatory mediators that effectively distinguished LC from healthy individuals. Lower concentrations of these mediators were associated with better cognitive performance. Collectively, these findings suggest a post-acute compensatory cytokine response in LC, potentially linked to cognitive outcomes and supporting these mediators as candidate biomarkers for neurological symptoms in the condition.	 CONTACT barros.tgr@gmail.com elianacbtoscano@ufjf.br @gpnitufjf ALZHEIMER'S ASSOCIATION AAIC 26
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