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Cytokines as factors associated with persistent post-COVID-19 headache: a case-control study

Djanino Fernandes da Silva, Pedro Augusto Sampaio Rocha Filho

Federal University of Pernambuco, Recife, Pernambuco, Brazil

Djanino Fernandes da Silva
contato@djanino@gmail.com

Introduction
Post-COVID-19 persistent headache is the most prevalent neurological manifestation of long COVID, affecting up to 26% of infected individuals. Dysregulation of pro-inflammatory and anti-inflammatory cytokines has been proposed as a key mechanism underlying symptom persistence, yet direct evidence comparing cytokine profiles between patients with and without headache persistence remains scarce.

Objective
To compare plasma levels of IL-6 and IL-10 between patients with persistent post-COVID-19 headache and those whose headache resolved after the acute phase.

Methods
Case-control study nested in a prospective cohort of patients who reported headache during acute COVID-19 (RT-PCR confirmed). Cases (n=20) maintained headache more than two years after infection; controls (n=40) were matched by sex, age, and time since infection. Plasma IL-6 and IL-10 were measured by flow cytometry (CBA kit, BD Biosciences). Headache impact, anxiety, and depression were evaluated using the Headache Impact Test (HIT-6) and The Hospital Anxiety and Depression Scale (HADS). Statistical analysis used Mann-Whitney U test and Spearman correlation (SPSS v.30).

Results
Groups were comparable in age (cases: 53.25±9.21 years; controls: 53.58±9.67), sex (80% female), and BMI. In the case group, 90% of headaches met ICHD-3 criteria for migraine, with bilateral (70%), pulsatile (85%) character, associated with photophobia (95%), nausea (90%), and phonophobia (90%). All cases fulfilled criteria for New Daily Persistent Headache (NDPH). Headache frequency averaged 78 days in the preceding 3 months, with median intensity 7/10; 70% reported medication overuse. HIT-6 score was significantly higher in cases (65.6±5.37 vs. 45.9±5.67; p<0.001). Cases showed markedly higher anxiety (HADS-A median: 12 vs. 6; p<0.001) and depression scores (HADS-D median: 10 vs. 5.5; p<0.001). Plasma IL-6 was elevated in cases (median 5.00 pg/mL; IQR 3.48–9.18) versus controls (2.69 pg/mL; IQR 2.44–3.66; p<0.001). IL-10 was also higher in cases (5.14 pg/mL; IQR 4.86–5.36 vs. 4.74 pg/mL; IQR 4.48–4.91; p=0.002).

Conclusion:
Persistent post-COVID-19 headache presents a migraine-like phenotype with severe functional impact, high rates of medication overuse, and significant psychological burden. Elevated IL-6 and IL-10 levels support a chronic neuroinflammatory state as a key underlying mechanism. These findings highlight the need for targeted immunological and clinical approaches in managing this disabling condition.

Keywords:
Neuroinflammation
Long COVID
Post-COVID-19 headache
New daily persistent headache
Cytokines

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