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CSF BIOMARKER EVIDENCE OF SYNAPTIC DYSFUNCTION IN ACUTE, BUT NOT POST-ACUTE COVID-19

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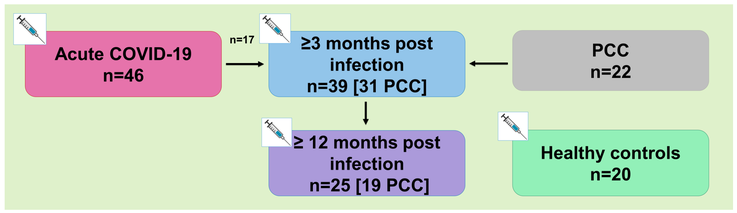
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- **Several CSF biomarkers of CNS pathology were altered during acute, but not post-acute COVID-19**
- **We found no association between (mild or moderate) neurocognitive PCC and CSF biomarkers of neurodegeneration**

Background

CNS immune activation and neurocognitive symptoms are common in severe COVID-19, but mechanisms of persisting CNS dysfunction in post COVID-19 conditions (PCC; "long covid") are unclear[1-2]. We used a panel of CSF markers, several of whom have been implicated in Alzheimer's disease (AD) and other neurodegenerative diseases[3-5] to investigate synaptic and lysosomal dysfunction in acute and post-acute COVID-19.

Study Design



- Cross-sectional analysis utilizing 2 longitudinal cohorts and healthy controls ("never COVID")
- CSF was drawn during acute COVID-19, ≥3 and/or ≥12 months post-acute infection
- Neurocognitive PCC symptoms at follow-up was evaluated by interview + self-report questionnaire

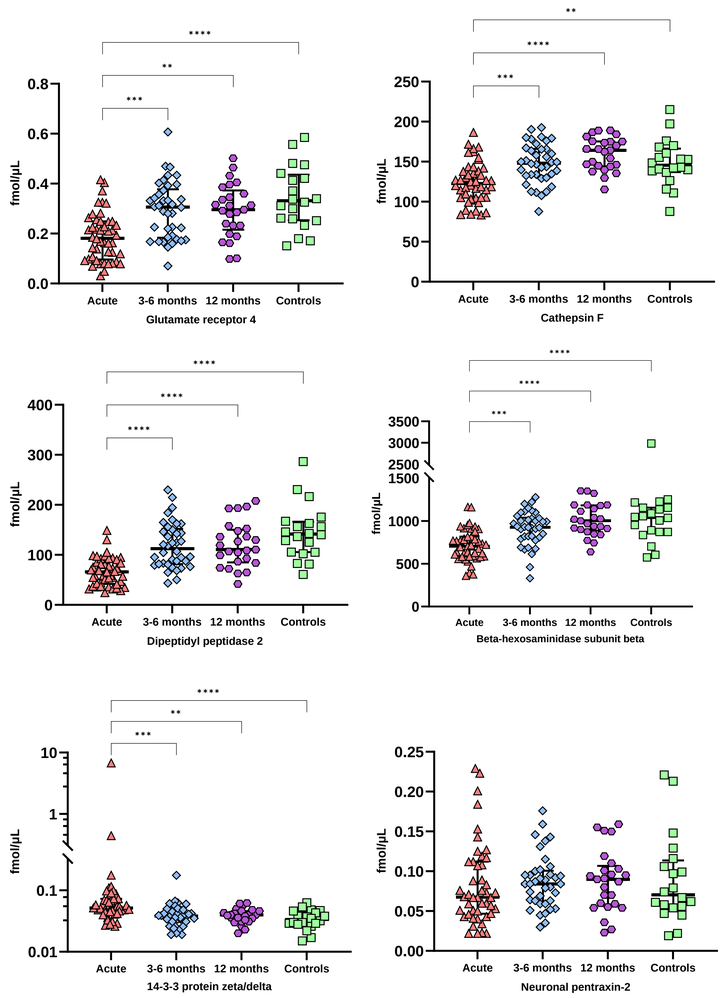


Figure 1. CSF concentrations of selected biomarkers across study groups

Significant alterations of a subset of synaptic and lysosomal CSF biomarkers were observed during acute COVID-19. Notably, neuronal pentaxin-2 remained unaffected.

Group comparisons of biomarker concentrations were analyzed by Kruskal-Wallis (Dunn's post hoc) test.

Conclusions

Several markers previously associated with neurodegenerative and psychiatric diseases were significantly altered during acute COVID-19. Notably, neuronal pentraxin-2 (a sensitive marker of cognitive decline in AD) remained unaffected. Importantly, no biomarker evidence of persisting CNS pathology was seen at follow-up either between patients and controls, or between patients with or without PCC indicating that mild or moderate PCC is not associated with progressive postinfectious neurodegeneration.

Results

- Patients had mild (15), moderate (hospitalized with oxygen; 33) or severe (ICU; 28) COVID-19
- Self-reported PCC symptom severity was mild or moderate
- Significant alterations of GRIA4, DPP-2, cathepsin F, HEXB (all decreased) and 14-3-3 zeta/delta (increased), were seen in acute compared with post-acute COVID-19 and controls (all p<0.005 [***Figure 1***]). No significant differences were seen for the other included biomarkers (data not shown).
- No significant differences in any biomarkers were seen between patients and controls, or between patients with PCC compared with fully recovered patients after the acute phase of COVID-19 at ≥3 or ≥12 months post acute infection.

Methods

We used a 37-marker CSF panel including cathepsins, calsyntenins, contactins, granins, glutamate receptor 4 (GRIA4), VGF, APP, neurogranin, syntaxins, LAMPs, beta-hexosaminidase subunit beta (HEXB), GM2A, dipeptidyl peptidase 2 (DPP-2), NCAM2, NSF, synapsin-1, CAMK2A, Thy-1, VAMP2, AP2B1, complexins, synucleins, GDI-1, neuronal pentraxins, PEBP-1, and members of the 14-3-3 protein family.

A micro-high performance liquid chromatography mass spectrometry system (6495 Triple Quadrupole LC/MS system, Agilent Technologies) equipped with a Hypersil Gold reversed-phase C18 column (dim.=100 × 2.1 mm, particle size=1.9 μm, Thermo Fisher Scientific) was used for quantitation.

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