Reply to "CSF Cytokine Profiles Do Not Reliably Delineate Encephalopathy and Inflammation in Neuro-COVID"

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In reply to Drs Finsterer and Scorza's comments, patients presented diverse cerebrospinal fluid (CSF) profiles regarding markers of neuroinflammation and neurodegeneration, and biochemical and cellular findings, even among patients with the same neurological condition.[1] The same applied to inflammatory cytokines. On average, CSF and serum cytokine patterns were distinct, which underscored the chronology of events triggering neurological manifestations.[2] CSF elevation of cytokines in inflammatory neurological diseases (IND) did not reflect a respective increase in serum. Conversely, encephalopathy was associated with higher serum interleukin 6, C-X-C motif chemokine ligand 8 (CXCL8), and transforming growth factor β1 levels, but cytokines in the CSF did not differ from controls in most cases.[2] An altered blood–brain barrier and a traumatic spinal tap could influence these results. However, red blood cell (RBC) counts in the CSF were adequate (4 RBC/mm^3, interquartile range = 0–33), except for 2 patients with encephalopathy with 2,048 and 5,547 RBC/mm^3. Their exclusion, however, did not alter the findings. Thus, CSF cytokine profiles were not influenced by serum contamination. Moreover, a correlation analysis showed that CSF and serum levels of cytokines were independent, except for CXCL10 in patients with encephalopathy (Table), which was not altered as compared to controls.[2] Patients were organized by their primary neurological manifestation at the time of CSF collection. One patient was diagnosed with neuromyelitis optica, but anti–aquaporin 4 was not tested. Patients with refractory headache presented normal brain magnetic resonance imaging (MRI), but 85% had CSF opening pressure > 200mmH_2O, and half had idiopathic intracranial hypertension (>250mmH_2O).[3] Seizures and abnormalities on electroencephalogram were considered for diagnosis of both encephalopathy and encephalitis. However, to avoid overlap between groups, encephalopathy was disregarded whenever signs of acute brain inflammation were present, including pleocytosis and/or brain MRI changes, which instead characterized encephalitis. Although headache may precede encephalopathy or IND, sequential onset between encephalopathy and IND can be ruled out in our study, because such conditions presented as first manifestations within 14 days from the onset of COVID-19. Therefore, CSF findings were unlikely to be associated with distinct stages of the same disease. Lastly, prospective analysis of patients would illuminate the dynamics of cytokines and biomarkers of inflammation. However, the study was conducted between April and June 2020, at the beginning of the COVID-19 epidemic in Brazil, which complicated the establishment of a structured cohort. Nevertheless, cytokine profiles defined at early stages of neuro-COVID indicated that events triggering neuroinflammatory syndromes originated from within the central nervous system,[2] even when SARS-CoV-2 was not detected in the CSF.[1,4]

TABLE. Correlation between CSF and Serum Levels of Cytokines

Groups	IL-2	CXCL10	CCL2	CXCL8
Headache				
Spearman *R*	−0.406	0.371	−0.371	−0.029
p	0.425	0.497	0.497	0.957
Encephalopathy				
Spearman *R*	0.235	0.664	0.315	0.224
p	0.462	0.022[a]	0.319	0.484
IND				
Spearman *R*	0.296	0.045	−0.218	0.527
p	0.378	0.903	0.521	0.100

Patients with COVID-19 and refractory headache, encephalopathy, and IND were evaluated for the dependency between serum and CSF levels of inflammatory cytokines previously assessed.[2] The analysis was performed with Spearman rank of correlation test for cytokines with detectable levels in paired CSF and serum in at least half of the individuals in each group. The analysis was carried out for IL-2, CXCL10, CCL2, and CXCL8. Spearman *R* and *p* values are shown.

[a]Significant at $p < 0.05$.

CCL2 = C-C motif chemokine ligand; CSF = cerebrospinal fluid; CXCL = C-X-C motif chemokine ligand; IL = interleukin; IND = inflammatory neurological diseases.

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Potential Conflicts of Interest

Nothing to report.

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References

1. Espíndola OM, Brandão CO, Gomes YCP, et al. Cerebrospinal fluid findings in neurological diseases associated with COVID-19 and insights into mechanisms of disease development. Int J Infect Dis 2021;102:155–162.
2. Espíndola OM, Gomes YCP, Brandão CO, et al. Inflammatory cytokine patterns associated with neurological diseases in coronavirus disease 2019. Ann Neurol 2021;89:1041–1045.
3. Silva MTT, Lima MA, Torezani G, et al. Isolated intracranial hypertension associated with COVID-19. Cephalalgia 2020;40:1452–1458.
4. Espíndola OM, Siqueira M, Soares CN, et al. Patients with COVID-19 and neurological manifestations show undetectable SARS-CoV-2 RNA levels in the cerebrospinal fluid. Int J Infect Dis 2020;96:567–569.

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