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CEREBRO-SPINAL FLUID FINDINGS IN NEURO-COVID

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Letter to the Editor

Dear Editor,

with interest we read the review article by Lewis et al. about the cerebro-spinal fluid (CSF) findings in patients infected with SARS-CoV-2 who manifested clinically with neuro-COVID [1]. It was found that the CSF was positive for SARS-CoV-2 RNA in only 6% of the patients with neuro-COVID and that only 12% had developed intrathecal anti-SARS-CoV-2 antibodies [1]. It was concluded that though neuro-invasion of SARS-CoV-2 and intrathecal antibody synthesis are rare [1], CSF biomarkers may have diagnostic, therapeutic, and prognostic benefit [1]. The review is appealing but raises the followin1g comments and concerns.

SARS-CoV-2 may not only enter the central nervous system (CNS) by retrograde transport of the virus along axons of the fifth and tenth cranial nerves but also along the seventh and ninth cranial nerves. The seventh cranial nerve is the cranial nerve most frequently affected in COVID-19. Cranial nerves may be affected in the course of cranial nerve involvement in Guillain-Barre syndrome (GBS) or isolated without affection of peripheral nerves. Furthermore, the virus may reach the CNS not only via these nerve routes but also via hematogenic spread and crossing of the blood brain barrier (BBB) [2].

Interestingly, the review does not mention the results of CSF lactate levels. CSF lactate may not only be elevated in case of inflammation, but also in case of seizures, hereditary disease, in particular mitochondrial disorders (MIDs), or due to lactate increasing drugs. Since neuro-COVID may manifest with seizures and CNS inflammation, it is crucial to evaluate also CSF lactate levels.

There is also no general discussion about CSF glucose in COVID-19 patients. Missing is the evaluation of the CSF for anti-ganglioside antibodies. GQ1b and GD1b antibodies may be elevated in the CSF in Miller-Fisher syndrome [3]. Anti-GD2/GD3 antibodies may be elevated in SARS-CoV-2 associated myelitis [4].

There is no evaluation of the opening pressure on spinal tap. Since SARS-CoV-2 infected patients may develop papilledema [5], it is crucial to know in how many of the patients with neuro-COVID the opening pressure was increased. Particularly in patients with multisystem inflammatory syndrome in children (MIS-C) an increased intra-cranial pressure has been reported [6]. The opening pressure may be also elevated in patients with venous sinus thrombosis, a complication of neuro-COVID increasingly recognised [7]. Venous sinus thrombosis may be due to SARS-CoV-2 associated hypercoagulability.

The pathogenesis of neurological manifestations in SARS-CoV-2 infected patients is more widespread than only “hypoxia, stroke, toxic-metabolic causes, the parainfectious inflammatory response, or

direct neuro-invasion" [1]. COVID-19 patients frequently develop coagulopathy, particularly hypercoagulability and thus develop thrombosis of cerebral veins [7]. neuro-COVID may also manifest as acute hemorrhaghic, (necrotic) leukoencephalitis (AHLE, AHNE)) [8,9], intracerebral hemorrhaghe, or as subarachnoid bleeding, being attributed to the tropism of SARS-CoV-2 to the endothelial lining, to coagulopathy, and therapeutic anticoagulation [10].

Missing is a discussion about the influence of the current medication (e.g. metformin, steroids, immune-modulators) on CSF findings. Missing are also comorbidities (e.g. diabetes, neuro-immunologic disease) and their influence on CSF composition. It should be discussed that SARS-CoV-2 can damage the cellular and humoral immune system resulting in superinfections and secondary neurological disease.

Concerning figure 2 we disagree with the notion that psychosis and encephalopathy are neurological symptoms, as indicated in the caption of the figure. They should be rather regarded as neurological disorders. Ataxia is not a neurological symptom either but a sign assessed by the investigating physician.

Overall, the review by Lewis et al. has several limitations which should be addressed to further increase the discussion. Missing is an analysis of intrathecal antiganglioside antibodies, CSF glucose, CSF lactate, and the opening pressure. Missing is a discussion about SARS-CoV-2 induced coagulopathy, about the neurotoxicity of anti-COVID-19 drugs, and about the attack against the immune system with secondary superinfections also affecting the CNS.

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