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# Does Endothelial Vulnerability in OSA Syndrome Promote COVID-19 Encephalopathy?



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**ABBREVIATIONS:** OSAS = OSA syndrome

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COVID-19 causes extrapulmonary manifestations that include severe neurologic complications, such as acute encephalopathy.<sup>1</sup> COVID-19 encephalopathy has various clinical expressions that range from subtle cognitive disturbances to coma, but its physiopathologic mechanism is not fully understood.

Previous reports have put forward the hypothesis of both systemic and cerebral endotheliitis that may be responsive to high-dose glucocorticoids.<sup>2</sup> We observed in a cohort of patients with COVID-19 encephalopathy who were hospitalized at Geneva University Hospitals (Switzerland) an increased prevalence of gadolinium enhancement in large arteries on brain MRI (90.6%) that was suggestive of underlying endotheliitis and an increased cerebrospinal fluid/plasma albumin ratio that was suggestive of blood-brain barrier dysfunction. Pathologic findings among patients with COVID-19 also found multisystemic endotheliitis that included cerebral arteries.<sup>2</sup>

In patients with COVID-19, older age, cardiovascular disease including hypertension, and obesity are known risk factors for poor clinical outcomes and a need of advanced respiratory support.<sup>1</sup> OSA syndrome (OSAS) shares the same landscape of comorbidities.

Interestingly, the presence of OSAS has been associated with COVID-19 infection and severity, with a higher risk of the development of respiratory failure, although a clear causal relationship has not been established.<sup>3</sup> Despite a high prevalence in the specific multimorbid population with severe forms of COVID-19, OSAS remains widely underdiagnosed.<sup>3</sup>

In a meta-analysis, OSAS was associated independently with an increased risk of endothelial dysfunction with a dose-response relationship between the severity of intermittent hypoxia and endothelial dysfunction (endothelial dysfunction was assessed by peripheral arterial tonometry in this meta-analysis; however, endothelial integrity was not directly evaluated in the cerebral circulation).<sup>4</sup> OSAS-induced intermittent hypoxia leads to a proinflammatory and a prothrombotic immunologic state, which causes endothelial dysfunction.<sup>4,5</sup>

Because OSAS and severe COVID-19 share at-risk clinical presentations and synergistic intermediary

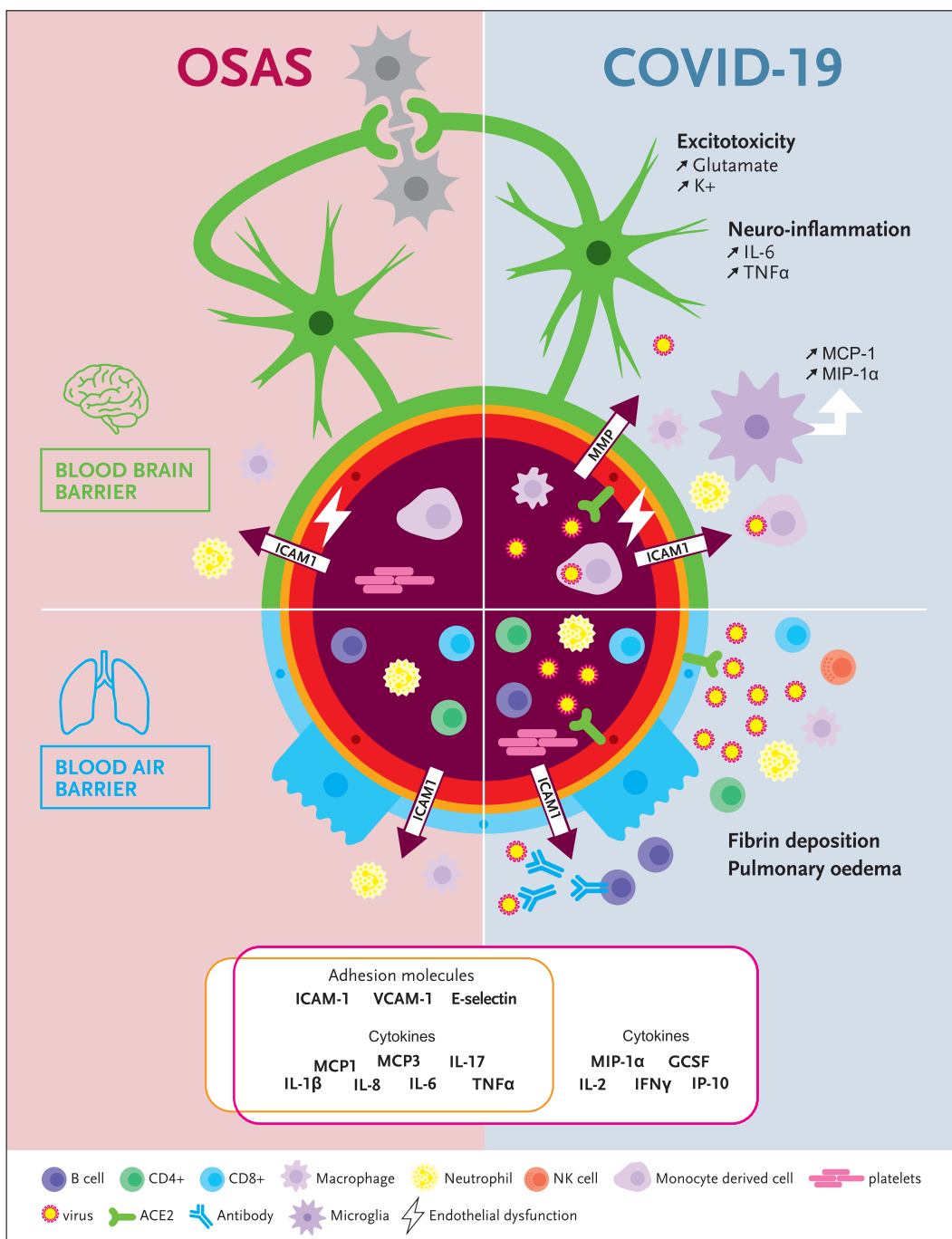


Figure 1 – Immune system modulation and endothelial changes of the blood-brain barrier and the blood-air barrier comparison of OSA syndrome and COVID-19-related encephalopathy. ACE2 = angiotensin-converting enzyme-2; GCSF = granulocyte colony-stimulating factor; ICAM1 = intercellular adhesion molecule-1; IFN $\gamma$  = interferon gamma; IP-10 = interferon gamma-inducible protein (IP) 10 or CXCL10; MCP-1 = monocyte chemo-attractant protein-1 (or CCL2); MIP-1 $\alpha$  = macrophage inflammatory protein 1-alpha; OSAS = OSA syndrome; TNF $\alpha$  = tumor necrosis factor alpha.

mechanisms that trigger endothelial injury, we hypothesized that patients with OSAS who are infected by SARS-CoV-2 may be at higher risk of COVID-19 encephalopathy. An untreated OSAS with preexisting neurovascular inflammation might favor encephalopathy development.

### Hypotheses and Discussion

In the lung, rapid SARS-CoV-2 replication is associated with reduced and delayed interferon-gamma signaling, which leads to an inflammatory monocyte-macrophage accumulation and an impaired T-cell response. These perturbations of the immune system response lead to a

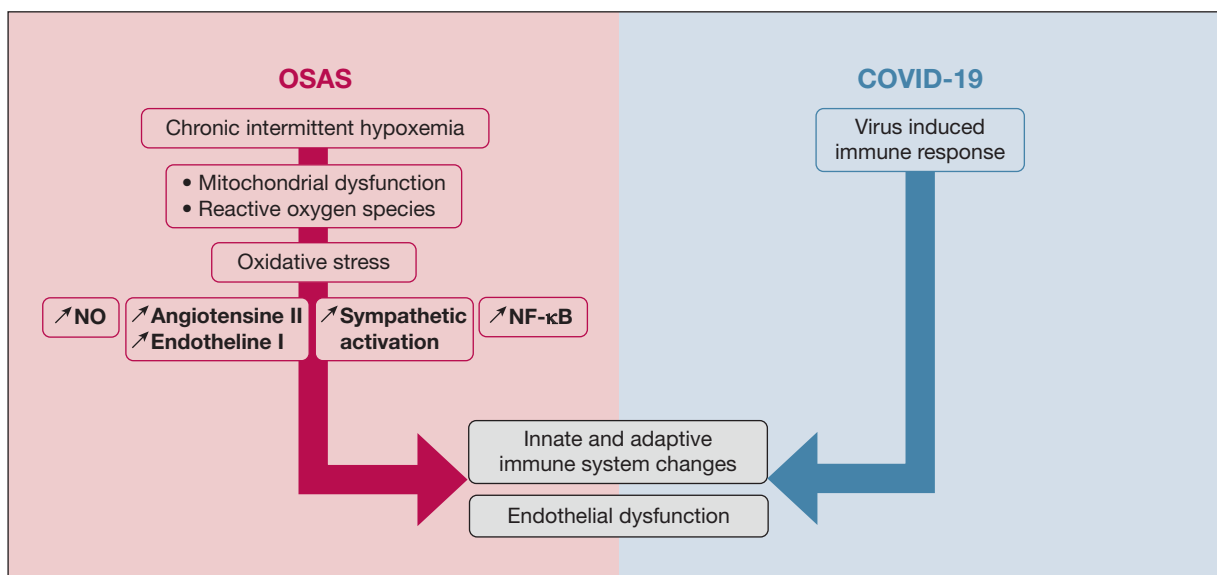


Figure 2 – Immune system changes and endothelium dysfunction in both OSA syndrome and COVID-19. NF- κB = nuclear factor κB; OSAS = OSA syndrome.

massive production of proinflammatory cytokines. In severe COVID-19, the so-called “cytokine storm” (or hypercytokinemia) in correlation with a sustained innate and adaptive immune system dysregulation, provoke diffuse vascular damage with molecular and cellular leakage and prevent the necessary immunologic balance for an optimal SARS-CoV-2 neutralization (Fig 1). All these inflammatory mechanisms result in diffuse endothelial injury that start in the lungs and then spread to multiple organs, thus causing a severe COVID-19 event. The “cytokine storm” with high levels of circulating proinflammatory molecules maintains a global hyperinflammatory state that might cause an acute encephalopathy. Both direct and indirect mechanisms may explain the endotheliitis found in patients with COVID-19 encephalopathy. Patients with COVID-19 encephalopathy present a similar phenotype to patients with OSAS, such as male sex, obesity, and a prevalence that increases with age.<sup>1,4,5</sup>

Untreated OSAS provokes a proinflammatory and prothrombotic state, which may facilitate endothelial injury and dysfunction, atherosclerosis, and thrombosis.<sup>5</sup> The leukocyte phenotype changes involve both innate and adaptive immunity. Monocyte-derived cells and neutrophils display a proinflammatory phenotype with a prolonged lifespan (decreased proapoptotic/antiapoptotic protein balance) that contribute to increased avidity for endothelial cells. Lymphocytes also acquire an activated proinflammatory

phenotype (especially  $\gamma\delta$  T cells) with an increased intracellular content of proinflammatory cytokines, decreased intracellular content of the antiinflammatory cytokine IL-10, increased adherence molecule expression, and higher cytotoxicity (CD8+ T cells) towards endothelial cells.<sup>5</sup> Repair endothelium capacity is also dysfunctional in patients with OSAS who have low circulating levels of nitric oxide, which is another key player, with vasodilatation, antiinflammatory, antioxidant, antiadhesive, and antithrombotic (down-regulating the expression of adhesion molecules in leukocytes, platelets, and endothelial cells) properties.<sup>4,5</sup> Patients with OSAS who are untreated display higher endothelial cell oxidative stress and inflammation and higher levels of circulating endothelin-promoting chronic endothelial injury.<sup>5</sup>

The combination of oxidative stress, metabolic changes, and proinflammatory phenotype probably leads to endothelial dysfunction and injury in both OSAS and COVID-19 (Figs 1, 2). The challenge is how to demonstrate the association between OSAS and COVID-19 encephalopathy. Based on the aforementioned arguments, OSAS is responsible for blood vessel wall disturbances that lead to increased permeability caused by endothelial cell disruption and impaired recycling. We hypothesized that this preexisting vascular vulnerability positions patients with OSAS at a higher risk of the development of severe SARS-CoV-2 inflammatory-related

complications, including COVID-19 encephalopathy. The synergic effect of the chronic diffuse vessel wall fragility and proinflammatory state encountered in patients with OSAS, in association with the acute COVID-19 inflammatory burst, potentiate the blood-brain barrier disruption and the invasion of COVID-19-induced inflammatory substrate into the CNS.

To illustrate our hypothesis, a previous study collected data on OSAS in the context of delirium/encephalopathy in patients with severe COVID-19. In a cohort of 140 patients with COVID-19, 118 patients (84.3%) presented with delirium or an abnormal neurologic examination. Of these, 15 patients (12.7%) had a comorbid OSAS in the delirium or abnormal neurologic examination group, whereas only one of 22 patients (4.5%) had a comorbid OSAS in the no-delirium and normal neurologic examination group.<sup>1</sup> These observations are consistent with a suspected clinical association between OSAS and COVID-19 encephalopathy. However, the severity of OSAS and the treatment of OSAS (type, adherence, and efficacy) were not reported in this study. These factors may influence the relationship between OSAS and COVID-19 encephalopathy. Furthermore, this association is probably underestimated because OSAS is underdiagnosed. Further studies are crucial to confirm the correlation between OSAS and COVID-19 encephalopathy because OSAS might be an actionable risk factor to target.

## Conclusion

Based on observations of patients with COVID-19 at our institution, we hypothesize that OSAS creates a proinflammatory condition that weakens blood vessel endothelium, including in the brain. Chronic OSAS-related inflammation may contribute to disrupt the blood-brain barrier balance, thus exposing the brain to systemic inflammation that may pave the route for CNS injuries. Thus, OSAS, a frequent and underdiagnosed comorbidity, could be a susceptibility factor for the development of COVID-19 encephalopathy. Future studies should confirm this hypothesis by studying the prevalence of OSAS in COVID-19 encephalopathy.

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