

Headache, Encephalopathy and Covid-19: Insight to the Physiology of the Neurological Involvement

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Abstract

Coronavirus targets the human respiratory system, but also the central nervous system, which expresses angiotensin converting enzyme 2. We present a case of a patient with COVID-19, progressive headache, encephalopathy and minimum respiratory symptoms, who recovered with the use of systemic steroids. We discuss about the probable mechanism underlying the encephalopathy, theorizing the role of CD8 lymphocytes in its pathogenesis.

Keywords: headache, encephalopathy, COVID-19, CD8 lymphocytes

Introduction

Coronavirus targets the human respiratory system, but it also has neuroinvasive capabilities and can spread from the respiratory tract to the central nervous system (CNS)(1). The most frequently reported neurological symptoms are myalgia, headache, anosmia, and ageusia, but less frequent thus more severe manifestations like stroke, encephalopathy/encephalitis, Guillain-Barré syndrome and skeletal muscle involvement are getting noticed due to the possible sequelae (2). We report an interesting case of encephalopathy in a COVID-19 positive patient.

Clinical Case

60-year-old female, obese, heavy smoker, sedentary, with medical history of hypertension, hypothyroidism, bipolar disease and celiac disease. No history of migraine. She reported close contact with a COVID-19 positive patient and five days after she developed mild but progressive headache with dizziness; no respiratory symptoms. On the third day of her symptoms, she reported dysarthria, diplopia and vomiting, so she was admitted in the clinic. No fever, anosmia or ageusia. Her neurological exam revealed bradipsychia, mild dysarthria, multidirectional nystagmus and diplopia in the horizontal left gaze. Complementary work-up: Brain CT and DWI MRI sequences were negative for stroke or brain hemorrhage, brain MRI reported normal, COVID-19 PCR positive, cerebrospinal fluid (CSF) with no increase in protein levels or IgG levels, normal CSF/serum quotient but 12 cells – lymphocytes – in the CSF, viral CSF meningitis panel negative, CSF PCR for COVID-19 negative, CSF ELISA for COVID-19 IgG negative, plasma IgG – SARS COV-2 positive, normal blood count, normal C-reactive protein, normal TSH levels, Thorax TC compatible with mild COVID-19 pneumonia, 2 hours electroencephalogram with global theta-delta activity. She was observed for 2 days, where she did not develop any respiratory symptoms but the headache and neurological symptoms kept getting worse, non-responsive to symptomatic treatment, so 1gr of methylprednisolone for 3 days was started with oral prednisone tapering. She progressively improved with the steroids, being discharged from the clinic 1 week after admission.

Results & Discussions

Critically ill patients of COVID-19 suffer from multiple organ failure (circulatory failure, sepsis, shock, renal failure, hepatic failure, coagulopathies, and respiratory failure) due to the intense inflammatory response against the virus that triggers a cytokine storm (2). COVID-19 is neurotropic and the hypoxic and metabolic insults in these patients subsequently result in diffuse brain dysfunction, helping the virus to enter into the brain (1, 2). The virus uses angiotensin converting enzyme 2 (ACE2) as a receptor for cell entry. Today we know ACE2 is expressed by endothelial cells but also the brain expresses ACE2 receptors on glial cells and neurons and it is especially prominent in the brainstem, the paraventricular nucleus, nucleus tractus solitarius, and the rostral ventrolateral medulla (3).

The speculated route of entry to the brain is via the olfactory system, where it may spread to the brain across the cribriform plate because the olfactory mucosa has a relatively high expression of ACE2 receptor (1). Also the virus can circumvent the blood-brain barrier and enter the brain through vascular endothelium or maybe the virus can reach the brain by trojan horse mechanism via infected leukocytes migration across the blood-brain barrier and cause the central nervous system dysfunction (2).

The patient is obese and a heavy smoker which are known risks factors to severe covid-19 (4). The relation of smoking and especially nicotine as a risk factor to neurological involvement of COVI-19 is pending of the evidence that the viral target receptor ACE2 is expressed in the brain and functionally interacts with nAChRs (3). The nicotine stimulation of the nAChR was found to increase ACE2 expression within neural cells and astrocytes (especially in the hypothalamus and brain stem). ACE2 signaling pathway is believed to counteract oxidative stress and neuroinflammation, so its disruption may lead to neurodegeneration of dopaminergic neurons impairment (dopaminergic vulnerability) in cholinergic pathways which might participate in cerebral hypoperfusion and in the progression of cognition decline that patients refer (3, 5).

Uginet et al (6) reported a cohort of 707 patients infected with COVID-19. Interestingly, the severity of the pneumonia was not associated with severity of the COVID-19 encephalopathy as in our case. The most frequent symptom was headache (60%) and patients with severe versus mild COVID-19 encephalopathy tended to present more often corticospinal tract signs at neurological examination (53.8%) with no mention to cerebellar or brainstem syndromes as in our case. Brain MRI abnormalities were reported in 92.0% of patients, with 85% of intracranial vessel gadolinium enhancement; an increased cerebrospinal fluid/serum quotient of albumin suggestive of blood-brain barrier disruption was reported in 85.7%. Reverse transcription PCR for COVID-19 was negative for all patients in the CSF as it was in our case. Interestingly, in this cohort the CSF biological findings as increased CSF/serum quotient, CSF white blood cell count within normal range, and the absence of direct proof of COVID-19 in the CSF were in favor of an indirect (or inflammatory) effect of COVID-19 for explaining this encephalopathy. Nevertheless, our patient only had increased cellularity in the CSF with no protein or CSF/serum quotient with good response to steroids which support the indirect inflammation theory (7). Even more, other groups suggest that steroids play a role normalizing CSF cytokines mediated by a hyperinflammatory mechanism and the cytokine storm. To clarify the exact pathological pathways and the role in cytokines and cells after the neurological involvement of COVID-19, we need precise and targeted documentation of neurological symptoms, but specific and sensitive attempts to isolate SARS-CoV-2 from cerebrospinal fluid from COVID-19 patients (1).

Finally, it is known that COVID-19 specific T cells are recruited from a randomly formed and pre-constituted T cell pool capable of recognizing specific viral epitopes. Specific CD4+ T cells are important for eliciting potent B cell responses that result in antibody affinity maturation. Spike-specific CD4+ T cells are found in patients with COVID-19, 30–50% of healthy people with no detectable COVID-19 infection also had COVID-19-specific CD4+ T cells and 20% had CD8+ cytotoxic T cells (8). Perivascular and parenchymal infiltrates of T cells have been detected in the brain of patients with COVID-19 (9). CD8+ T cells are essential to control viral clearance from resident glia by secreting IFN- γ , granzyme B, and perforin. CD8+ T cells enter the parenchyma and CD4+ T cells accumulate around blood vessels. This trafficking difference is due to the expression of tissue inhibitor of MMPs (TIMP-1) by CD4+ T cells (9). So probably, the majority of the lymphocytes found in the CSF of our patient were CD8+ T cells and they were the major responsible or contributors to the encephalopathy with their cytotoxic activity in their attempt to clear the virus from the brain (event though we failed to detect with regular COVID-19 PCR assay).

Conclusion

The patient developed progressive neurological symptoms with alteration in the electroencephalogram. We failed to show actual COVID-19 or COVID-19 antibodies in her CSF. The COVID-19 PCR was positive and also her IgG plasma levels for COVID-19, so we can argue that the neurological symptoms were due to the systemic COVID-19 infection (indirect inflammation), but the exact origin of the neurological symptoms is the field of our hypothesis because she was never critically ill or exhibited systemic inflammation but developed encephalopathy and progressive headache that only responded to steroids. Our main hypothesis, regarding our findings and her response is that the CSF tests are not sensitive as the nasal test or the blood detection for neutralizing antibodies. We could not find increased protein levels or increased IgG levels in the CSF and maybe this is because the patient developed the neurological symptoms very early in the COVID-19 infection stage, and so were the CSF tests.

The only finding was the lymphocytes in the CSF that we know are part of the adaptive response to the viral infection during the first week (8). According to the timeline of the infection, we can presume that these were T cells that reacted to COVID-19, more specific CD8+ T cells that migrated through the brain blood barrier to clear intra CNS COVID-19; the bias to this hypothesis is that we are assuming according to the COVID-19 known immune response. We could not do flow cytometry to the CSF in order to categorize the T cells. We need to further work in our viral detection techniques in the CSF and also see if these were T or B cells or if they had a cytotoxic profile to provide better insight to the encephalopathy and the actual benefit of the steroids (when to use them).

Conflict of Interest

The authors declare no conflict of interest

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