Encephalopathy and Cytotoxic Lesion of the Corpus Callosum Associated with Cytokine Storm in COVID-19: A Case Report

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Introduction

Unlike adults, the vast majority of children with COVID-19 have mild symptoms in the acute, infectious phase of the disease, but a small minority of children becomes severely ill. MIS-C patients often present with multi-organ dysfunction that manifests late in the course of SARS-CoV-2 infection and most are positive for SARS-CoV-2 IgG antibodies [3]. This hyper inflammatory syndrome shares features with Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome, primarily a cytokine-mediated process. On the contrary, some studies have questioned the role of cytokine storming in COVID-19-induced organ dysfunction [4,5]. The cytotoxic lesions of the corpus callosum (CLOCC) are associated with a heterogenous group of conditions. It typically manifests in children and can present with encephalopathy, nuchal rigidity, and seizures [6,7]. CLOCC is thought to be caused by a cytokine-mediated neuroinflammation as a result of the BBB disruption. While CLOCCs were previously reported in adult and pediatric patients with COVID-19 [8-10], so far there has not been strong laboratory evidence of a cytokine storming involved in the pathogenesis of COVID-19 associated CLOCCs.

Case Report

A previously healthy 12-year-old male presented to the emergency department (ED) after 3 days of fever, abdominal pain, nausea/vomiting and 2 days of frontal headache which he described as dull and achy. He was febrile at home to Tmax 102F. He was brought in after a witnessed episode of altered mental status where on waking, he was able to articulate words but did not make logical sense. He returned to baseline after approximately 5 minutes. In the ED, he was tachycardiac with intermittent fever. Subsequent labs at admission or
Neurology was consulted for abnormal head movements described as intermittent neck extension. Differential diagnosis included diaphragmatic irritation (i.e., hiccups) versus myoclonus, rather than an epileptic nature. Neurologic exam was notable for diffuse hyperreflexia yet negative Babinski signs. Due to a concern for ADEM (Acute disseminated encephalomyelitis), MRIs of the brain and cervical spine with and without contrast were obtained. While the spine MRI was unremarkable, the brain MRI showed a restricted diffusion area in the splenium of the corpus callosum without contrast enhancement, consistent with a Cytotoxic Lesion of the Corpus Callosum (CLOCC) [11] (shown in Figure 2). Lumbar puncture was not attempted due to coagulopathy. Patient was treated with two rounds of intravenous immunoglobulin (IVIG, 2 mg/kg), IV methylprednisolone (1 mg/kg every 6 hours), heparin drip initially then transitioned to Lovenox. He was discharged on low dose aspirin, oral prednisone taper, and to continue PT/OT. He never required anti-seizure drugs during the 10 days hospitalization course. On 6-week follow-up, he had reassuring cardiac assessment, normal EKG and echocardiogram. The ongoing headaches were consistent with migraine. His involuntary jerking movements were suggestive of tics. Otherwise, he had recovered well.

Discussion

Our patient has probably a concurrent adenovirus infection; however, his clinical evolution and neurological complications are not typical for adenovirus infection [12]. CLOCC is a non-specific finding associated with a variety of etiologies [13], and has been reported in adult and pediatric patients with COVID-19, but in children predominantly observed in MIS-C patients [2,8,10]. A hypothesized mechanism of this non-ischemic lesion involves the vulnerability of the oligodendrocytes-rich splenium to markedly increased levels of cytokines and extracellular glutamate [11]. High levels of circulating IL-6 and sIL2R seen...
in our patient have provided evidence of cytokine storming and T-cell activation in the pathogenesis of COVID-19 related encephalopathy and CLOCCs. Indeed, several studies have shown a positive association of IL-6 and sIL2R levels with the disease severity, at least in adult patients with COVID-19 [14,15]. Notably, our patient recovered well following the immunomodulatory therapy, not requiring cytokine antagonists such as Tocilizumab. This observation aligns with the overall outcome discrepancy between adult and pediatric COVID-19 patients.

Whether there is a causative cytokine level in the cerebrospinal fluid (CSF) in COVID-19 patients presenting with CNS complications remains to be investigated. Interestingly, literature search has revealed no case report of FIRES (Febrile Infection-Related Epilepsy Syndrome) after COVID-19 infection despite the cytokine storming and innate immunity activation. Our patient has recovered during acute phase following immunomodulatory therapy; however, the effects of cytokine storming and neuroinflammation on long-term neurodevelopmental outcomes and even risk for chronic epilepsy require a longitudinal follow-up.

Declaration of Conflicting Interest

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References


