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Autoimmune Encephalitis Following COVID-19 Infection with Brain Magnetic Resonance Imaging Mimicking Metachromatic Leukodystrophy in an Adolescent: A Case Report

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ABSTRACT

Neurological manifestations such as encephalitis, ataxia, headache, seizure, papilledema, and ophthalmoplegia have been reported in several pediatric Coronavirus Disease 2019 (COVID-19) studies. There are multiple pathogeneses that may underlie the clinical manifestations. Herein, we reported a case of adolescent with clinical manifestation like encephalitis with positive Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) antibody, and suspected Metachromatic Leukodystrophy (MLD) in brain Magnetic Resonance Imaging (MRI) finding. The patient did not respond to corticosteroid therapy but showed clinical improvement over intravenous immunoglobulin (IVIG) therapy. The possibility of COVID-19 infection in neurological disorders should be considered in pediatric patients.

Keywords: encephalitis, COVID-19, adolescent, IVIG

INTRODUCTION

Neurological manifestations have been reported in several pediatric COVID-19 studies.[1] Recent study found that 3.8% of children, and adolescents (52/1334 children) have neurological symptoms while confirming positive COVID-19. The manifestations include epileptic state 13.5%, encephalitis 9.6%, *Guillain-Barre* syndrome 9.6%, acute demyelinating syndrome 5.7%, chorea 3.8%, psychosis 3.8%, isolated encephalopathy 3.8%, and transient ischemic attack 1.9%.[2] There are multiple pathogeneses that may underlie the symptoms, such as retrograde transsynaptic spread, increased permeability of blood-brain-barrier (BBB), chronic persistent hypoxia, activation of the intravascular coagulation cascade, and increase of intravascular pressure.

Major diagnostic criteria of encephalitis/encephalopathy are altered mental status for over 24 hours without an alternative cause. Minor diagnostic criteria are fever ≥ 38^{o}C within 72 hour before or after presentation of symptoms, generalized or partial seizure not fully attributable to a preexisting seizure disorder, new onset of focal neurological findings, in addition of neurologic dysfunction (seizure, focal neurologic findings, cerebrospinal fluid pleocytosis ≥ 5 white blood cells/µL, abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset, and abnormality electroencephalogram (EEG). It was two for possible, and ≥3 for probable or confirmed encephalitis[3]. The specific diagnostic for encephalitis caused by COVID-19 can be based on cerebrospinal fluid (CSF)

polymerase chain reaction (PCR) antibody or serum antibody. A reported largest cohort of patient with COVID-19, and neurological symptoms who underwent lumbar puncture in the early of pandemic. In all of cases, RT-PCR for SARS CoV-2 from CSF was negative. CSF analysis findings, including WBC were normal in most patient with COVID-19.[4] However, another systematic review by Ariane Lewis et al, found that seventeen out of three hundred twenty one (6%) patients was PCR positive, and seven out of fifty eight (12%) patients showed positive antibodies.[5]

Management of encephalitis is basically supportive. If herpes simplex encephalitis is suspected, acyclovir intravenous can be given. If autoimmune encephalitis is suspected, first line therapy is corticosteroid or/and intravenous immunoglobulin (IVIG). Methylprednisolone can be given 30 mg/kg/day (max 1 gr/day). IVIG can be given alone or in conjunction with IV corticosteroid with a dose of 2 gr/kg divided over the course of 5 days.[6]

CASE REPORT

A 12 years old adolescent was admitted to our emergency department with chief complaint of paralysis on all extremities 27 days before admission. The symptoms preceded by subfebrile fever, nausea, and vomiting. Later, the patient became restless, and chattering, could no longer speak adequately, screamed unclearly, and could not sleep, and communicate with others. There was no history of seizure, and cephalgia. History of COVID-19 vaccination, and infection was denied. Patient had history of fever, behavioral changes, and paralysis on lower extremities followed by upper extremities at nine months before admission. Then patient became quiet, pensive, and not cheerful. These symptoms relieved in two months. On physical examination, the patient was delirium, blood pressure was 110/70 mmHg, pulse rate was 91 beats per minute, respiratory rate was 20 breaths per minute, and the temperature was 36.8°C. The patient's nutritional status was obese. The pupil was isochoric, and nystagmus was positive. Meningeal sign was negative. Physiological reflex was increased, and Babinski group was positive. There was spastic, and no clonus. Muscle strength was decreased on both side extremities, and sensory was difficult to assess.

Brain Computed Tomography (CT) Scan showed brain atrophy. Then, the patient was diagnosed with suspected autoimmune encephalitis differential diagnose with multiple sclerosis. Patient was planned to do brain MRI with contrast, and lumbar puncture. A high dose of methylprednisolone 30mg/kg/day was administered for three days. There was partial improvement in motoric, but no mental status. On the third day of high dose, the patient had adverse effect, gastrointestinal bleeding. Day 4, brain MRI showed hyperintense lesions on T2W/FLAIR, and isointense on T1W in the bilateral lateral periventricular region of the white matter, and bilateral deep white matter with impression of a suspected metachromatic leukodystrophy (MLD) (figure 1). Immunoglobulin G (IgG) SARS CoV-2 antibody test was reactive. Patients did not meet the criteria of multisystem inflammatory syndrome in children (MIS-C). Cerebrospinal fluid analysis was at the normal limit, and CSF PCR SARS-CoV-2 was negative. Due to the limitations of the antibody test panel in our center, we can only test for anti-NMDA receptors with negative results The electroencephalogram (EEG) showed severe hypofunction of brain activity. Nerve conduction study showed demyelinating and axonal neuropathy.

Treatment of IVIG 2 gr/kg divide in 5 days was start in this patient. By the day 10, there was improvement in mental status, and patient began to understand conversation, responds appropriately, and spasticity was decreased. She was discharged with fully conscious. Follow up after 3-month patient was fully conscious, and there was gradual improvement in movement.

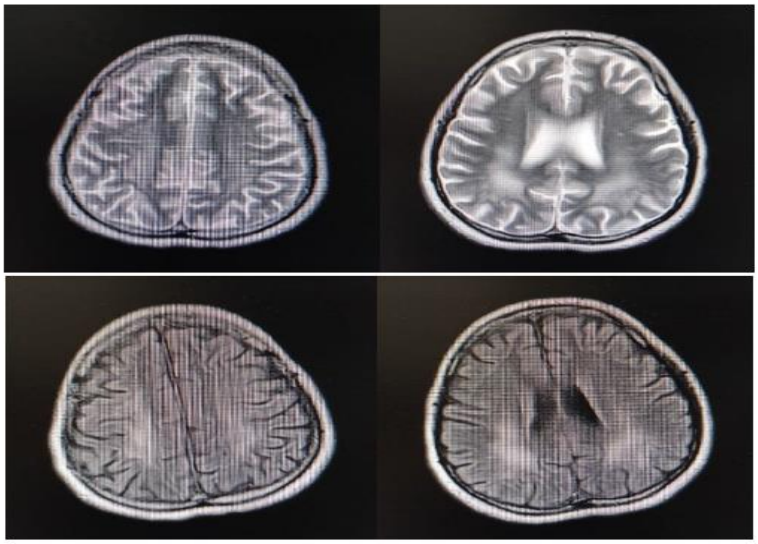

Figure 1. Hyperintense lesion on periventricular, white matter bilateral, and deep white matter on T2W, and FLAIR (axial plane)

DISCUSSION

In a systematic review study by Lauren et al, stated that encephalitis or encephalopathy occurred in 34% of COVID-19 or MIS-C paediatric patient. They also found that male, and female sex ratios were not significantly different (64% vs 46%). But several case report such as Vraka et al, Kahwagi et al, Bur et al, and Miranda et al found cases all of encephalitis/encephalopathy occurred in female.[7] In our patient we meet criteria of encephalitis such as altered mental status, focal neurological change (paralysis), fever, and EEG changes which fulfills probable encephalitis.[3]

More recently, Graus et al developed diagnostic criteria and algorithm for possible autoimmune encephalitis such as (1) subacute onset over less than 3 months of working memory, altered mental status pr psychiatric symptoms, confusion, disturbed sleep (2) at least one of the following: new focal CNS findings, seizure not explained by preexisting disorder, CSF pleocytosis, and/or MRI feature suggestive of encephalitis, and (3) reasonable exclusion of alternative causes. Based on the algorithm, our patient met the criteria for probable autoimmune encephalitis however we could not perform an autoimmune antibody panel examination and a follow-up MRI to see improvement. Then this patient's diagnosis lead to probable autoimmune encephalitis rather than ADEM with still reconsider other diagnosis.[8] This patient actually still met the criteria for Acute Disseminate Encephalomyelitis (ADEM) according to other literature, but the clinical situation was more likely autoimmune encephalitis, where the patient's condition was more severe and did not respond to corticosteroids at baseline. ADEM show rapid improvement than autoimmune encephalitis. The MRI findings in this patient are also inconsistent with the general ADEM findings, where the lesions are multifocal, not diffuse like the MRI findings in this patient.[9]

There are multiple pathogenesis underlie central nervous system (CNS) involvement COVID-19 infection. SARS-CoV-2 can transport endocytosis or exocytosis via retrograde transsynaptic, and axonal transport of vesicles along microtubules. It also can travel from the olfactory bulb to the olfactory tubercle, and cortex, and/or to the brain stem, and medulla. It can invade CNS across vascular endothelial cells, which express angiotensin-converting enzyme-2 (ACE-2) receptors, or by the passage of virus-infected leukocytes through BBB. It also can infect lymphocytes, granulocytes, and monocytes. It can invade CNS across vascular endothelial cells, which express ACE-2 receptors, or by the passage of virus-infected leukocytes through BBB, known as

the Trojan Horse mechanism.[10] Increased permeability of BBB caused by systemic inflammation in COVID-19 infection might allow passage of the infected immune cells, and thereby virus entry into CNS.[11] Respiratory distress or failure can result in chronic persistent hypoxia that can cause neurological injury.[12] Severe COVID-19 infection with cytokine storm can cause vascular leakage, activation of complement, and coagulation cascade proceeding disseminated intravascular coagulation, and cause injury to CNS.[13] SARS-CoV-2 binding to endothelial ACE-2 receptor may increase luminal pressure in the vessels, which may cause bleeding in the brain, and also abnormalities in the coagulation system, such as thrombocytopenia, and increased levels of d-dimer contributed to intracerebral bleeding or thrombus.[14] The CNS has a dense parenchymal structure and the usual lack of permeability of its blood vessels is a barrier to virus invasion. However, if a virus gains access to the CNS, it is difficult to remove. Nerve cells lack major histocompatibility complex antigens therefore, viral elimination depends on the action of cytotoxic T cells. Furthermore, neuronal apoptosis after virus infection is first choice and may also exert a relatively protective effect.[15]

Brain MRI in this patient showed symmetrical lesions in the periventricular, and white matter. These MRI images lead to many differential diagnoses especially symmetrical periventricular regio such as MLD, Hashimoto encephalopathy, Sjögren-Larsson syndrome, and others.[16] Brain MRI findings of encephalitis associated with COVID-19 infection vary widely. Abdel et al, found the MRI findings was hyperintense lesions on T2 signal symmetrically.[17] This may resemble the MRI findings in MLD. In early form, the central, and periventricular white matter are first affected. As the disease progresses, subcortical structures of white matter may also be affected. In extremely severe cases, projection fiber damage as well as the appearance of a "tigroid pattern" (bands that are associated with the preservation of myelin in the perivenular areas) are observed. The corpus callosum may also be affected.[18] Our patient met the clinical criteria of MLD but in the course of the disease, the patient showed clinical improvement with immunotherapy which was not found in MLD, which was progressive, and irreversible.[18] Meanwhile, patient did not meet the criteria for clinical manifestations of Hashimoto encephalopathy, and Sjögren-Larsson syndrome. So we thought this case was an autoimmune encephalitis with rare brain MRI imaging.

Moreover, to trace the involvement of the COVID-19 infection in this patient, we conducted a nerve conduction study. The result showed myopathic change, sensory and motor demyelination. In study by Omar et al, those who tested positive for COVID-19 either with PCR or antibody had abnormality in EMG examination, it was found three out of four patients had myopathic change. This further strengthens the involvement of COVID-19 in these patients. When compared with ADEM, there was no involvement of the peripheral nervous system.[17]

An update on autoimmune encephalitis (AE) treatment on 2018 stated that first line therapy of AE was corticosteroid, and IVIG. We found improvement on motoric but not on the cognitive function. IVIG can be given alone or conjunction with IV corticosteroid with a dose of 2 gr/kg divided over the course of 5 days, but can be given over 2 days.[19] Abdel et al reported that two of four pediatric COVID-19 with encephalopathy (altered consciousness) were treat with IVIG (1 -2 gr/kg). All of them show improvement in consciousness but partial in motoric.[17] It our patient, initial treatment with corticosteroid showed improvement in motor function but not in consciousness., and after IVIG therapy, patient showed improvement in consciousness, and gradual improvement in motoric.

Our patient shows improvement, consciousness, and intelligence function

after treatment with corticosteroid, and immunoglobulin. Vrake et al report two case with encephalitis associated with COVID-19, showed complete recovery in consciousness in both of case, complete motoric function in first case, and there was residual paralysis right upper limb in the second case.[20] Another case report by Kahwagi et al, there was recovery of consciousness, behavior, and motoric function after two months follow-up.[21] Abdel et al also report four pediatric patient with encephalopathy associated with COVID-19, there was resolved in consciousness at 11^{th}-32^{th} hospitalization. This serial case did not include medium term follow-up in the study, but all of the patient discharged still had problem with motoric function.[17]

CONCLUSION

COVID-19 infection has a broad spectrum of clinical symptoms. Unexplained encephalitis should be screened for COVID-19 infection, and imaging, especially MRI. Atypical MRI imaging can mimic other diseases. Initial treatment with immunotherapy will result in clinical improvement.

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