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Pediatric Autoimmune Encephalitis Following COVID-19 Infection

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Abstract

Similar to the pathogenesis of autoimmune disease, SARS-CoV-2 (COVID-19) infection has been shown to be associated with dysregulated and persistent inflammatory reactions and production of some antibodies. We report 3 pediatric patients found to have serum SARS-CoV-2 antibodies who presented with neurologic findings suggestive of postinfectious autoimmune-mediated encephalitis. All 3 cases showed lymphocytic pleocytosis on cerebrospinal fluid studies and marked improvement in neurologic symptoms after high-dose intravenous corticosteroids. The manifestations of SARS-CoV-2 infection in the pediatric population are still an evolving area of study, and these cases suggest autoimmune-mediated encephalitis as yet another SARS-CoV-2 related complication.

Keywords

COVID-19, autoimmune, encephalitis, pediatrics, postinfectious

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Introduction

The immunopathogenicity of SARS-CoV-2 (COVID-19) infection and that of autoimmune disease share similar characteristics. A recent review conducted by Liu et al highlights some of these similarities in the immunologic profile and associated organ injury noted with SARS-CoV-2; evidence of cross-reactivity between the virus and the host's innate and adaptive immune responses, presence of autoantibodies and immune-mediated disorders in those with active or recent infection, and other examples of molecular mimicry and dysregulated immune responses that is seen with primary autoimmune diseases.[1] Specific cases of autoimmune-mediated transverse myelitis found both during and after SARS-CoV-2 infection along with cases of Guillain-Barre syndrome following SARS-CoV-2 infection have been noted mostly in adults.[2-4] In this series, we present 3 cases of patients presenting with postinfectious autoimmune-mediated encephalitis after mild or asymptomatic SARS-CoV-2 infection. The first case presented with signs and symptoms of acute meningoencephalitis and was subsequently diagnosed with optic neuritis versus neuropathy when he developed visual impairment. The second case was an adolescent with autism spectrum disorder who presented with new-onset seizures and had cerebrospinal fluid findings consistent with encephalitis. The third case presented with seizures and subacute headache. Prior SARS-CoV-2 infection was the only potential trigger found in these individuals. All 3 cases fulfilled clinical, laboratory, and electrographic criteria for antibody-negative autoimmune encephalitis following SARS-CoV-2 infection with excellent response to steroids. These cases add to the evolving spectrum of neurologic complications associated with SARS-CoV-2 infection in the pediatric population.

Case 1

A 6-year-old boy developed fatigue, headache, and fevers after arriving in Tijuana, Mexico. His headaches were initially relieved with acetaminophen but persisted even after he returned to Los Angeles, California. Over the next 12 days, he was evaluated in 3 different emergency departments for his symptoms. His laboratory tests were significant for low sodium (127 mmol/L) and elevated C-reactive protein (72 mg/

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L) with a normal head computed tomography (CT). He was diagnosed with a viral illness and possibly even meningitis but ultimately discharged because he was thought to be too well appearing. He then developed urinary retention, lower extremity weakness, and ataxic gait before arriving at our emergency department. He was afebrile but significantly distressed with examination, which was significant for a positive Brudzinski sign, difficulty consistently following simple commands, photophobia (dilated fundus examination showed bilateral grade II disc edema), and refusal to ambulate despite intact strength in all extremities. Laboratory tests were significant for leukocytosis (white blood cell [WBC] count 14.6 $\times$ $10^3/\mu L$), elevated inflammatory markers (erythrocyte sedimentation rate 38 mm/h, C-reactive protein 9.4 mg/L), positive SARS-CoV-2 serum antibody but negative SARS-CoV-2 polymerase chain reaction (PCR) from nasopharyngeal swab and cerebrospinal fluid, negative meningoencephalitis cerebrospinal fluid PCR panel for other organisms, and lymphocytic pleocytosis on cerebrospinal fluid studies with elevated opening pressure (48 cm H_2O). Initial brain magnetic resonance imaging (MRI) showed mild focal fluid-attenuated inversion recovery hyperintensity and leptomeningeal enhancement in bilateral parietal and temporal lobes consistent with meningitis. His headache and transient visual symptoms (difficulty focusing on objects, darkening vision) improved after lumbar puncture and initiation of acetazolamide. He was also able to ambulate independently with mild residual ataxia at discharge.

Unfortunately, he was readmitted within 24 hours with recurrent headaches, worsening visual symptoms, and new relative afferent pupillary defect in his right eye. Repeat brain MRI and orbits revealed flattening of optic nerve insertion sites within posterior globes with protrusion and significant edema of optic nerves (right greater than left). Previous areas of fluid-attenuated inversion recovery hyperintensity and leptomeningeal enhancement were not reassessed in this study. Acetazolamide was continued but with more frequent dosing and repeat lumbar puncture showed improved opening pressure (29 cm H_2O) and pleocytosis. Cerebrospinal fluid cytology was negative for malignancy, SARS-CoV-2 antibody, and pediatric central nervous system autoimmune antibodies including serum myelin oligodendrocyte glycoprotein and cerebrospinal fluid *N*-methyl-D-aspartate (NMDA) receptor antibodies.

Given slowly improving indolent meningitis with still elevated intracranial pressure, there was concern for a postinfectious autoimmune process causing optic neuritis. Thus, high-dose intravenous methylprednisolone (30 mg/kg/d) was given for 3 days. The patient's visual symptoms appeared mildly improved, and his headaches and ataxia had completely resolved afterward. He was discharged with oral prednisone taper over 4 weeks and decreased acetazolamide dose for 2 weeks. At follow-up, he no longer had signs of disc edema but was prescribed glasses, with no other symptoms concerning for encephalitis.

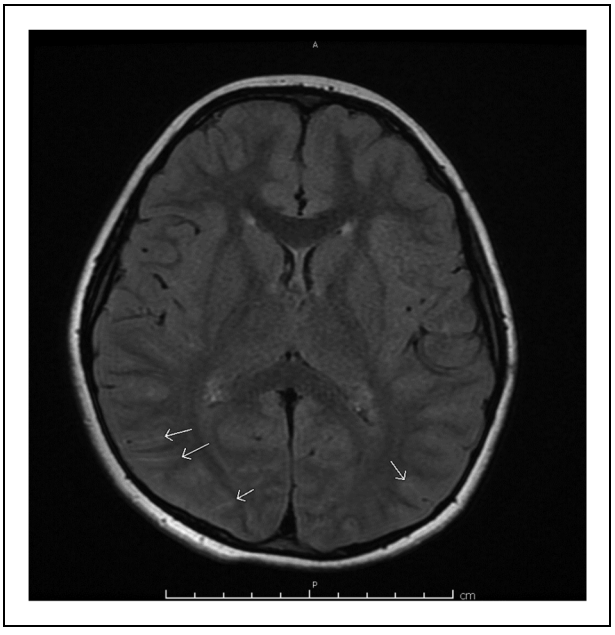

Figure 1. Brain magnetic resonance imaging (#MRI) showing T2 fluid-attenuated inversion recovery areas of hyperintensity in bilateral parietal lobes.

Case 2

A 12-year-old boy with autism spectrum disorder and intellectual disability presented after a generalized tonic clonic seizure without active infectious symptoms but with some maternal concern for subtle behavioral changes. He had diarrhea for 2 days the week prior but was never febrile. On admission, he was febrile and postictal but arousable and with a nonfocal neurologic exam. During the hospitalization, he experienced a second generalized tonic clonic seizure that was aborted with lorazepam. He was also loaded with levetiracetam and continued on maintenance dosing. His laboratory tests were significant for mild leukocytosis (WBC 11.3 $\times$ $10^3/\mu L$), mildly elevated inflammatory markers (platelets 546 $\times$ $10^3/\mu L$, C-reactive protein 4.2 mg/L), lymphocytic pleocytosis and negative SARS-CoV-2 antibody and negative meningoencephalitis PCR panel on cerebrospinal fluid studies, positive SARS-CoV-2 antibody in the serum. Serum NMDA receptor antibody was negative. Brain MRI showed 3 incidental arachnoid cysts, whereas electroencephalogram was consistent with diffuse slowing. Given protein elevation in the cerebrospinal fluid out of proportion to the level of pleocytosis, with negative infectious workup, there was concern for a postinfectious inflammatory central nervous system process so high-dose intravenous methylprednisolone (1 gm/day) was given for 3 days. He improved after the first dose with increased alertness and activity, answering simple questions and following simple commands. He was continued on levetiracetam at discharge for 1 month and then tapered off over 3 weeks. He remained seizure-free at follow-up 6 weeks later.

Case 3

A 12-year-old boy with a history of intermittent, bifrontal headaches presented with 2 afebrile, generalized tonic clonic seizures over a 5-day period. Both seizures were preceded by visual aura and headache, and they aborted after a few minutes without intervention. Head imaging and laboratory tests, including SARS-CoV-2 PCR from nasopharyngeal swab, were unremarkable after each seizure. An electroencephalogram after his second seizure revealed focal slowing over the left hemisphere. Levetiracetam was started for a new diagnosis of epilepsy with presumed unprovoked seizures, and the child was discharged home. However, he was readmitted a few days later owing to worsening headaches occurring multiple times per day and associated with photophobia. Brain MRI and MR venogram were unremarkable. Topiramate was started for dual management of presumed migraines and epilepsy with recommendations to taper off levetiracetam.

Over the next 4 days, he developed fevers, chills, and myalgias, with laboratory tests showing stable leukocytosis and mildly elevated erythrocyte sedimentation rate (14 mm/h). Remaining inflammatory markers (C-reactive protein, ferritin, D-dimer, procalcitonin, interleukin-6) were within normal ranges. Lumbar puncture showed lymphocytic pleocytosis. His infectious workup was positive for rhinovirus/enterovirus in the nasopharynx and SARS-CoV-2 antibody in the serum (his father had a viral illness about 5 months prior). Repeat brain MRI now showed new sulcal fluid-attenuated inversion recovery hyperintensity in bilateral frontoparietal lobes with diffuse leptomeningeal enhancement concerning for meningitis. The chronicity of his symptoms over 3 weeks along with new abnormal MRI findings raised concern for a postinfectious inflammatory process, so high-dose intravenous methylprednisolone (1 g/d) was given for 3 days. His headaches completely resolved afterward, and he remained seizure free at follow-up several weeks later, with recommendation to taper off topiramate. Cerebrospinal fluid anti-NMDA receptor antibody sent inpatient and serum myelin oligodendrocyte glycoprotein antibody sent after treatment with methylprednisolone were negative.

Discussion

These cases demonstrate an area not fully explored in the medical literature, specifically the postinfectious neurologic complications that can arise from SARS-CoV-2 infection in the pediatric population. The disease courses for these 3 patients give evidence to an autoimmune-mediated encephalitis following serologic evidence of prior SARS-CoV-2 infection. Although the presenting signs and symptoms of neurologic dysfunction were different in these children, all 3 eventually fulfilled criteria for encephalitis. Two patients developed new-onset seizures. All 3 patients had neuroimaging and cerebrospinal fluid findings suggestive of inflammation without active infection along with abnormal electroencephalograms.[5] The sustained clinical improvement after treatment with methylprednisolone also supports an autoimmune etiology of encephalitis. Although these cases did not fulfill CDC criteria for multisystem inflammatory syndrome in children as only 1 organ was involved, the immune modulating treatments recommended for multisystem inflammatory syndrome in children may have some role in these postinfectious autoimmune encephalitis cases.

Known Neurologic Complications Associated with COVID Infection

The manifestations and complications of SARS-CoV-2 infection in the pediatric population remains a developing area of investigation as the pandemic continues. Neurologic complications in particular have been reported across all ages. In the adult population, neurologic manifestations include headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and seizures, whereas febrile seizure and meningoencephalitis are more common in the pediatric population.[6,7] Arango et al reported on a 5-month-old who initially presented with fever, vomiting, and diarrhea, later developing seizures in the setting of a positive SARS-CoV-2 nasopharyngeal PCR.[8] Acute disseminated encephalomyelitis has also been described in pediatric patients associated with active SARS-CoV-2 infection and other variants of human coronaviruses.[9] The brain MRI findings for our 3 patients, however, did not fulfill acute disseminated encephalomyelitis criteria.[10]

Encephalitis appears to be a rare complication of SARS-CoV-2 infection. From the largest reported cohort of 1695 patients aged <21 years hospitalized with SARS-CoV-2 between March and December 2020, only 15 patients (of which nearly half were diagnosed with multisystem inflammatory syndrome in children) were found to have severe encephalopathy and only 8 patients had acute central nervous system inflammation concerning for encephalitis, aseptic meningitis, or acute disseminated encephalomyelitis.[9] It is not clear whether these patients received immune modulating treatment, if it was specifically given for a neurologic indication, or how they responded.

In another case series of adult patients admitted to a single medical center with SARS-CoV-2 infection, 15 patients (4.3%) had neurologic manifestations other than isolated anosmia and/or nonsevere headache.[11] Cerebrospinal fluid examination in 2 patients showed lymphocytic pleocytosis; one patient was ultimately diagnosed with anticontactin-associated protein antibody encephalitis and the other with meningopolyradiculitis. Three patients had cranial neuropathy with meningopolyradiculitis, brainstem encephalitis, or delirium and were all found to have increased serum titer of anti-GD1b antibodies implicating antiganglioside autoimmunity. SARS-CoV-2 antibody was not detected in the cerebrospinal fluid of any of the patients and neither was any underlying neoplasm. The authors concluded that cerebrospinal fluid lymphocytic pleocytosis and/or blood-brain barrier dysfunction in the setting of SARS-CoV-2 infection could be associated with parainfectious encephalitis and polyradiculitis. Even though neurologic disease was the first or only manifestation of SARS-CoV-2

infection in 6 of the 15 patients, there is no commentary on whether immune-modulating treatment was employed.

Autoimmune Encephalitis

Autoimmune causes of encephalitis have been found in all age groups. Although antibodies associated with paraneoplastic disease target mostly intracellular epitopes in adults, those associated with autoimmune encephalitis in children target cell surface proteins and receptors. These antibody targets impact synaptic transmission, causing neurophysiological dysfunction and inflammatory changes often fulfilling the diagnostic criteria of encephalitis. One of the most common autoimmune antibodies in the pediatric population is the anti-NMDA receptor antibody, which produces a distinct clinical constellation of encephalopathy, seizures, involuntary movements, autonomic instability, and psychiatric changes.[5] None of these cases had evidence of anti-NMDA receptor antibody, and the 2 patients tested for serum myelin oligodendrocyte glycoprotein antibody were negative. The patient in the first case received comprehensive testing for autoimmune antibody-positive encephalitis, whereas the workup in the subsequent cases was more limited as those patients did not demonstrate any neurologic signs or symptoms of recurrence during follow-up to justify further diagnostics. Thus, we concluded that our patients most likely manifested antibody-negative forms of autoimmune encephalitis in close temporal association with prior SARS-CoV-2 infection. Given the inherent immunogenicity of SARS-CoV-2[11,12] and the variability of SARS-CoV-2 neurologic manifestations, it would be prudent to investigate whether there are as of yet unidentified biomarkers that predispose patients toward developing autoimmune encephalitis following SARS-CoV-2 infection.

Outcomes in patients with autoimmune encephalitis range from full recovery, limited recovery in one-third of patients, to partial recovery in another third of patients. Importantly, delaying initiation of immune-modulating therapy can put these patients at risk for poorer outcomes.[5]

In the Setting of Multisystem Inflammatory Syndrome in children

Although complications of SARS-CoV-2 infection in pediatric patients are most often related to multisystem inflammatory syndrome in children, our cases did not fulfill the criteria of multisystem involvement. Per the Centers for Disease Control and Prevention (CDC) criteria, multisystem inflammatory syndrome in children should involve at least 2 organ systems including cardiac, renal, pulmonary, hematologic, gastrointestinal, dermatologic, or neurologic signs.[13] Our patients only demonstrated serious neurologic dysfunction with no clear involvement of other organs, though they fulfilled additional criteria for multisystem inflammatory syndrome in children including fever, nonspecific laboratory evidence of inflammation, and positive serologies suggestive of prior SARS-CoV-2 infection. The postinfectious autoimmune-mediated encephalitis noted in our patients could be considered a form of multisystem inflammatory syndrome in children that shares similar pathogenesis and treatment considerations, specifically timely immune modulation with high-dose corticosteroids.

Conclusion

These 3 cases provide evidence that antibody-negative autoimmune encephalitis could be a potential complication following SARS-CoV-2 infection in children. Although a temporal association with SARS-CoV-2 infection as evidenced by SARS-CoV-2 serum antibodies certainly does not imply a causal link to the subsequent autoimmune encephalitis diagnosed and treated in these patients, the absence of any other clear infectious or autoimmune source of central nervous system disease with the excellent, timely, and sustained response to steroids without remission or recurrence of neurologic dysfunction strongly point to this diagnosis of exclusion. As the pandemic continues, providers should consider that a postinfectious autoimmune-mediated encephalitis may be the sole manifestation following SARS-CoV-2 infection. Recognizing this potentially disabling complication should prompt consideration of immune modulating medications like high-dose corticosteroids once other etiologies have been ruled out.

Author Contributions

MH, MB, JH, and AP were all involved in conceptualizing and designing this case series. All authors were involved in the literature review and drafting of this manuscript. All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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