Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical Letter

N-Methyl-D-Aspartate Receptor Encephalitis Associated With COVID-19 Infection in a Toddler

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Introduction

Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is characterized by mood and behavior changes, seizures, abnormal movements, autonomic instability, and encephalopathy. It occurs most commonly in young adults. A paraneoplastic association has been made with ovarian teratoma, although this is rare in children.[1] More recently patients with anti-NMDAR encephalitis after viral infections have been reported, including herpes simplex virus (HSV), Japanese encephalitis virus, and now the 2019 novel coronavirus (SARS-CoV-2 or COVID-19).[2-5] We present the first pediatric patient with COVID-19–associated anti-NMDAR encephalitis.

Patient Description

This 23-month-old girl developed fever, fussiness, poor sleep, constipation, and decreased oral intake in July 2020. She was fully vaccinated and did not have a personal or family history of frequent infections. A week after onset of symptoms, she presented to the emergency department where she was noted to be dehydrated and febrile to 100.9°F. She appeared fussy, was not interacting with care givers, was no longer talking, and had nearly constant kicking and thrashing movements of her arms and legs. Polymerase chain reaction (PCR) screening for SARS-CoV-2 was positive. Two days after admission, she had several seizures, treated acutely with lorazepam and levetiracetam. Cerebrospinal fluid (CSF) analysis demonstrated a glucose of 56 mg/dL (serum 105 mg/dL), total protein 25 mg/dL, seven leukocytes/μL (89% lymphocytes and 11% monocytes), and two red blood cells/μL. The result of multiplex nested PCR in CSF was negative for *Escherichia coli, Streptococcus pneumoniae, Streptococcus agalactiae, Haemophilus influenzae, Neisseria meningitidis, Listeria monocytogenes, enterovirus, human parechovirus, HSV 1 and 2, varicella zoster virus, cytomegalovirus, human herpesvirus 6, Cryptococcus neoformans, and Cryptococcus gattii*. SARS-CoV-2 PCR from the CSF was negative. CSF oligoclonal bands and immunoglobulin G (IgG) index were not obtained. Serum c-reactive protein and erythrocyte sedimentation rate were normal. Magnetic resonance imaging of the brain with and without contrast was normal.

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Two weeks into the disease course, despite resolution of fever, she continued to have worsening encephalopathy and persistent hyperkinetic movements of the arms, legs, and head. Intravenous methylprednisolone (30 mg/kg/day) was administered for five days. Autoantibody testing demonstrated NMDAR-IgG positivity in the serum (1:640) and CSF (1:40). Repeat serum SARS-CoV-2 PCR remained positive and anti–SARS-Cov2 IgG resulted positive. Tetanus antibodies and pneumococcal IgG 23 indicated normal response to previous immunizations. Serology test results for Epstein-Barr virus, cytomegalovirus, Mycoplasma pneumoniae, and Bartonella were negative. Because of persistent encephalopathy, poor sleep, hyperkinetic movements, and mood lability, intravenous immunoglobulin 2 gm/kg was administered. Over the following week, abnormal movements and encephalopathy gradually resolved and she had returned to her baseline two weeks after being discharged from the hospital.

Discussion

Anti-NMDAR encephalitis is a known autoimmune or paraneoplastic condition. Although it has been linked to prior viral infections, such as HSV infection, and to tumors (most commonly ovarian teratomas), there may be no identified provoking factors. A recent observational study showed that patients with a history of anti-NMDAR encephalitis, but no history of HSV encephalitis, were more likely to be seropositive for anti–HSV-1 IgG (49% seropositivity versus 21% in age-matched control subjects). Antibody evidence of previous Epstein-Barr virus or cytomegalovirus infections was not significantly different between the two groups.[6] This suggests an increased risk of anti-NMDAR encephalitis after HSV-1 infection, even without clinically evident viral encephalitis. Additional mechanisms of indirect pathogenesis, such as molecular mimicry in which a viral epitope is structurally similar to an NMDAR epitope, may be explanatory. A similar indirect pathogenesis may exist in patients with coronaviruses such as SARS-CoV-2.

A postinfectious inflammatory condition after acute SARS-CoV-2, termed multisystem inflammatory syndrome in children (MIS-C), has been described. MIS-C typically presents four to six weeks after acute SARS-CoV-2 infection. A prospective and retrospective surveillance of children in the United States with MIS-C related to SARS-CoV-2 reported infrequent nervous system involvement.[7] Increased autoantibody production in children with MIS-C has been described.[8]

Two adults with anti-NMDAR encephalitis associated with SARS-CoV-2 have been reported.[5,9] Both patients showed significant recovery after immunotherapy with steroids and intravenous immunoglobulin. At the time of publication, the authors were unaware of other cases of anti-NMDAR encephalitis with recent SARS-CoV-2 infection in pediatric populations. As the understanding of both the neurological and non-neurological manifestations of SARS-CoV-2 in children is evolving, we report a child with SARS-CoV-2–associated anti-NMDAR encephalitis.

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