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Clinical Observations

SARS-CoV-2-Related Acute Necrotizing Encephalopathy of Childhood With Good Response to Tocilizumab in an Adolescent

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ABSTRACT

Background: Acute necrotizing encephalopathy of childhood (ANEC) is a rare parainfectious neurological disorder. ANEC is associated with a high mortality rate and poor neurological outcomes. ANEC is postulated to arise from immune-mediated or metabolic processes driven by viral infections. Although there have been some case reports of acute necrotizing encephalopathy with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coinfection in adults, paediatric cases are rare.

Methods: A single case report of SARS-CoV-2-related ANEC in an 11-year-old boy is presented through retrospective chart review. Literature search was performed using PubMed, Embase, Cochrane database, and Google Scholar to compare and analyze similar cases of parainfectious immune-mediated encephalopathies related to SARS-CoV-2 in children.

Results: An 11-year-old boy with acute SARS-CoV-2 infection presented with ophthalmoplegia, ataxia, and aphasia. Neuroimaging findings demonstrated significant swelling and signal changes in bilateral thalami, brainstem, and cerebellar hemispheres, consistent with ANEC. His high ANEC Severity Score indicated poor neurological prognosis. Treatment with a combination of early steroid therapy, intravenous immunoglobulin therapy, and targeted interleukin 6 (IL-6) blockade yielded good neurological improvements. Literature search identified 19 parainfectious immune-mediated encephalopathies related to SARS-CoV-2 in children. The only other pediatric ANEC case identified was postinfectious and thus not included.

Conclusions: This is the first report of a pediatric case of SARS-CoV-2-related ANEC, which responded well to early immunotherapy, including IL-6 blockade. Early immunotherapy with IL-6 blockade can be considered as an adjunct in managing severe ANEC.

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Introduction

Acute necrotizing encephalopathy of childhood (ANEC) is a rare parainfectious neuroinflammatory condition with poor prognosis. Diagnostic criteria of ANEC include an acute encephalopathy with rapid deterioration in consciousness following viral disease, absence of cerebrospinal fluid (CSF) pleocytosis, increased CSF protein, and characteristic neuroimaging findings of symmetrical, multifocal lesions in bilateral thalami, cerebral white matter, cerebellum, and brainstem.1 The prognosis of ANEC is poor: 30% mortality rate and less than 10% of survivors recovering fully.1

In recent years, we observed a broad spectrum of neurological manifestations associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).2 SARS-CoV-2-associated ANEC has been described in few adults and one child.3 SARS-CoV-2 can also trigger other immune-mediated neurological disorders including acute encephalitis, acute disseminated encephalomyelitis (ADEM), Guillain-Barre syndrome, myelin oligodendrocyte glycoprotein antibody disease, and anti-N-methyl-D-aspartate receptor encephalitis.4 In children, neurological complications in SARS-CoV-2-associated multisystem inflammatory syndrome were prominent, conferring significant risk of morbidity and mortality.1,5

Here, we review a case of pediatric ANEC with SARS-CoV-2 infection, presenting with ophthalmoplegia, cerebellar and brainstem dysfunction. Good clinical outcomes were achieved after combination immunotherapy, including interleukin 6 (IL-6) blockade. A literature review was performed using PubMed, Embase, Cochrane database, and Google Scholar to consolidate parainfectious conditions (within 2 weeks) immune-mediated neurological diseases in children (<18 years old) related to SARS-CoV-2. We included (1) acute encephalopathies caused by cytokine storms (ANEC, hemiconvulsion-hemiplegia-epilepsy syndrome, cytotoxic edema); (2) acute encephalopathies with convulsive status epilepticus (acute encephalopathy with biphasic seizures and late reduced diffusion, febrile infection-related epilepsy syndrome); and (3) demyelinating conditions (ADEM) in the acute phase of SARS-CoV-2 infection. We included case series and case reports, describing their presentation, treatment, and outcomes. We excluded patients with multisystem inflammatory syndrome as these are postinfectious conditions.

Patient Description

A previously well 11-year-old boy presented to the general practitioner with two days of fever, nausea, and vomiting without respiratory symptoms. SARS-CoV-2 antigen rapid test was positive, and he was discharged with symptomatic medications. One day later, he re-presented to the children's emergency with acute dizziness, slurred speech, left gaze deviation, progressively unsteady gait, and subjective weakness. SARS-CoV-2 infection was diagnosed in few adults and one child.3 His Glasgow Coma Scale score was 12 (E4V2M6), expressive aphasia, bilateral partial ptosis with ophthalmoplegia, bilateral cerebellar signs including dysdiadochokinesia, and past-pointing with mild truncal ataxia. He had normal tone and hyperreflexia in both knee and ankle jerks. Power was 5 (based on Medical Research Council grading) in both upper and lower limbs. His right eye was held in an adducted, downward gaze, whereas his left eye held a central, downward gaze, suggesting cranial nerves III and IV palsy, respectively. He was admitted to the pediatric intensive care unit due to his progressive neurological deterioration. Modified Rankin Scale (mRS) score was 4.

Diagnostic considerations included SARS-CoV-2-associated ANEC, ADEM, acute brainstem encephalitis, and Miller Fisher syndrome. Brain magnetic resonance imaging (Fig) showed swelling and signal changes involving bilateral thalami, midbrain, pons, cerebellar hemispheres, and periventricular white matter, correlating with a diagnosis of ANEC. Lumbar puncture revealed elevated CSF red cell count (25 cells/μL), elevated protein level (1.02 g/L), normal opening pressure, and no pleocytosis with normal glucose and lactate levels. Oligoclonal bands were absent. CSF meningoencephalitis infectious panel returned negative, including SARS-CoV-2 PCR. Extensive serum and CSF autoimmunity tests were negative, including anti-N-methyl-D-aspartate, anti-myelin oligodendrocyte glycoprotein, anti-glutamic-acid-decarboxylase, and anti-GQ1b-ganglioside IgG. Inflammatory markers were elevated: erythrocyte sedimentation rate 65 mm/hr, C-reactive-protein 36 mg/L, and procalcitonin 12.1 μg/L. However, ferritin levels and liver function tests were normal. Given these results, his ANEC Severity Score was 5 of 9, conferring high-risk for poor neurological outcome.6 Genetic susceptibility testing for RANBP2 mutation was not sent.

The patient was promptly initiated on immunotherapy with intravenous (IV) methylprednisolone 1000 mg daily for 5 days and intravenous immunoglobulin (IVIG) 2 g/kg over two days. He also received one dose of IV tocilizumab 8 mg/kg 12 hours from hospital presentation. Normothermia at 35°C to 36°C was maintained for six days. Serum sodium levels were kept minimally at 140 mmol/L for neuroprotection. He received a five-day course of IV remdesivir to treat SARS-CoV-2. Other concurrent antimicrobials included empirical IV ceftriaxone, azithromycin, acyclovir, and oseltamivir, until respective viral and bacterial studies returned negative.

After eight days, he demonstrated good response to treatment; Glasgow Coma Scale improved to 15, ophthalmoplegia and ataxia improved, and mRS score reduced to 2. He was discharged home after 16 days with residual deficits including mild ophthalmoplegia, upper limb dysmetria with intention tremor, mild aphasia, and dysarthria. At discharge, mRS score was 1. Two weeks later, mRS score improved to 0, indicating neurological function recovery.

Discussion

Parainfectious immune-mediated neurological disorders occur during the early infection phase, often progressing rapidly with no inciting pathogens identified in CSF. These disorders are broadly divided into acute encephalopathies caused by cytokine storms, acute encephalopathies with convulsive status epilepticus (possibly due to excitoxic brain damage), and acute demyelinating conditions.1 Common themes in management are largely supportive with neuroprotective techniques, antiepileptics, and immunotherapy with corticosteroids.1 The use of cytokine inhibitors including tocilizumab and anakinra in these conditions has been described as beneficial, although limited to small case series/reports.

Our literature search identified 19 parainfectious immune-mediated neurological disorders related to SARS-CoV-2 in children. There were seven cases of ADEM/ADEM-like conditions, four cases of cerebral cytotoxic edema, and eight cases of severe encephalopathies (Table).5,6-12 No cases of hemiconvulsion-hemiplegia-epilepsy, acute encephalopathy with biphasic seizures and late reduced diffusion, or febrile infection-related epilepsy syndrome were found in the acute phase of SARS-CoV-2 infection. The only other pediatric ANEC case was postinfectious, and thus not...
included. In the largest case series involving 11 cases, we were unable to obtain details of their presentation and treatment. Of the 19 cases identified, ages ranged from five days to 13 years. Main presenting symptoms include altered mental status, seizures, speech disturbances, or motor weakness within the first week of illness. In those with ADEM/ADEM-like disorders, half were treated with high-dose steroids and/or IVIG (three of five with treatment details). There were no mortalities, although three of seven had residual neurological deficits. In those with cytotoxic cerebral edema, mortality was 50%. In those with severe encephalopathies, three of eight died and two of eight had residual neurological deficits. No treatment with cytokine inhibitors was reported.

ANEC is a rare, fulminant, acute encephalopathy that primarily affects children after viral illnesses, commonly influenza A/B, human herpesvirus 6, herpes simplex virus, and measles. ANEC is postulated to arise from immune-mediated processes incited by viral infections, cytokine storm, hereditary susceptibility, and other unknown factors. Inflammatory cytokines like IL-6 and tumor necrosis factor-α are neurotoxic and increase blood-brain barrier vascular permeability, causing endothelial cell injury and myelin and oligodendrocyte necrosis. Cytokine storm and activation of other immune pathways have also been identified as key players in severe SARS-CoV-2 infection with high levels of serum tumor necrosis factor-α, IL-1β, IL-6, IL-12, and interferon gamma detected. Despite significant overlaps in the proposed pathogenesis of ANEC and severe SARS-CoV-2 infection, only few cases of SARS-CoV-2-related ANEC have been reported. The exact mechanisms of SARS-CoV-2-related neuronal injury in ANEC and interactions with potential genetic vulnerability in individuals warrant further investigation.

There was only one other case of SARS-CoV-2-associated ANEC described in a nine-month-old infant presenting with fever, drowsiness, and focal status epilepticus. SARS-CoV-2 IgG was positive, but IgM and PCR were negative, suggesting a post-infectious immune process around three weeks post-SARS-CoV-2 infection. Findings of brain magnetic resonance imaging were consistent with ANEC. He was treated with IVIG but unfortunately had poor neurological outcomes. In ANEC, current proposed treatment includes early steroid therapy, IVIG, and/or plasma exchange to dampen the effects of hypercytokinemia and hyper-permeability of the blood-brain barrier. However, neurological outcomes remain poor in severe ANEC. Second-line treatment options include therapeutic hypothermia and IL-blocking agents (tocilizumab).

The use of tocilizumab, an anti-IL-6 monoclonal antibody, was recently described to benefit children with severe ANEC.
TABLE
Parainfectious Immune-Mediated Diseases in Children With SARS-CoV-2

| Study | Number of Patients With Acute, Parainfectious Immune-Mediated Diseases | Sex; Age Range | Neurological Symptoms | Treatment | Outcome |
|-------|--------------------------------------------------------------------------|----------------|----------------------|-----------|---------|
| LaRovere et al<sup>1</sup> | Total n = 11 | Sex not specified. Severe encephalopathy: 7, Acute CNS infection/ADEM: 2, Acute fulminant cerebral edema: 2 | Not detailed | Not detailed | Severe encephalopathy: 3 died, 3 discharged, 1 new deficit |
| Lindan et al<sup>8</sup> | Total n = 4 | 3 M, 1 F; 2 months-13 years | ADEM-like: seizures, dystonic posturing, encephalopathy, headache | IVIG in 1 IV high-dose steroids in 1 | Normal in 4 |
| Vraka et al<sup>9</sup> | n = 1 | F: 10 years | Altered mental state, aphasia, right arm neglect | Supportive in 2 IVIG | Minimal motor deficits |
| De Miranda Henriques-Sauza et al<sup>10</sup> | n = 1 | F: 12 years | Acute motor weakness leading to flaccid tetraplegia, aphasia | IV methylprednisolone pulse × 2 Spastic tetraparesis |
| Fragoso et al<sup>11</sup> | n = 1 | M; 5 days | Seizures | High-dose steroids | Normal |
| Gaur et al<sup>12</sup> | n = 1 | M; 9 years | Altered mental state, dysarthria, ataxia | Symptomatic | Normal |

Abbreviations:
ADEM – Acute disseminated encephalomyelitis
CNS – Central nervous system
F – Female
IV – Intravenous
IVIG – Intravenous immunoglobulin
M – Male
SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

The patient’s high ANEC Severity Score prompted additional early immunomodulatory therapy with IV tocilizumab. He responded well, attaining full recovery after two weeks with no side effects to tocilizumab. Tocilizumab is generally safe in children, although infections, hypersensitivity reactions, and rarely gastrointestinal perforation may occur.<sup>15</sup>

This is the first time tocilizumab has been utilized in SARS-CoV-2-related ANEC. SARS-CoV-2-related ANEC is likely similar to other infection-associated ANEC. We extrapolated data from other infection-associated ANEC and propose that those with moderate or severe ANEC should be considered for second-line interventions like IL-6 blockade, with good outcomes in our case and previous cases.<sup>15</sup>

We highlight limitations to our recommendations including only a single patient in our report, overall small numbers of ANEC, and high likelihood of bias reporting. Therefore, decision for second-line treatment needs to be carefully measured and personalized, based on the patient’s symptom severity and potential side effects.

Conclusion

Pediatric ANEC related to SARS-CoV-2 remains a rare but potentially catastrophic condition. We demonstrated a severe case of parainfectious ANEC from SARS-CoV-2 infection who achieved favorable outcomes with combination therapy of early steroids, IVIG, and targeted IL-6 blockade. Further studies to better understand the pathogenic pathways resulting in neurological injuries related to SARS-CoV-2 would improve treatment modalities and clinical outcomes.

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References

1. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev. 1997;19: 81–92.
2. Aghogali G, Marin BG, Katchur NJ, et al. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care. 2021;34:1062–1071.
3. Lazarte-Rantes C, Guevara-Castañón J, Romero L, et al. Acute necrotizing encephalopathy associated with SARS-CoV-2 exposure in a pediatric patient. Cureus. 2021;13, e15018.
4. O’Loughlin L, Alvarez-Toledo N, Budrie L, Waechter R, Rayner J. A systematic review of severe neurological manifestations in pediatric patients with coexisting SARS-CoV-2 infection. Neurol Int. 2021;13:410–427.
5. LaRovere KL, Riggs BJ, Poussaint TY, et al, Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United...
States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536–547.
6. Yamamoto H, Okumura A, Natsume J, et al. A severity score for acute necrotizing encephalopathy. Brain Dev. 2015;37:322–327.
7. Mizuguchi M, Ichiyama T, Imataka G, et al. Guidelines for the diagnosis and treatment of acute encephalopathy in childhood. Brain Dev. 2021;43:2–31.
8. Lindan CE, Mankad K, Ram D, et al, ASPNR PECOBIG Collaborator Group. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health. 2021;5:167–177.
9. Vraka K, Ram D, West S, et al. Two paediatric patients with encephalopathy and concurrent COVID-19 infection: two sides of the same coin? Case Rep Neurol Med. 2021;2021, 6658000.
10. de Miranda Henriques-Souza AM, de Melo ACMG, de Aguiar Coelho Silva Madesso B, Freitas LF, Sampaio Rocha-Filho PA, Gonçalves FC. Acute disseminated encephalomyelitis in a COVID-19 pediatric patient. Neurol- ogy. 2021;81:141–145.
11. Fragoso DC, Marx C, Dutra BG, et al. COVID-19 as a cause of acute neonatal encephalitis and cerebral cytotoxic edema. Pediatr Infect Dis J. 2021;40: e270–e271.
12. Gaur P, Dixon L, Jones B, Lyall H, Jan W. COVID-19-Associated cytotoxic lesions of the corpus callosum. AJNR Am J Neuroradiol. 2020;41:1905–1907.
13. Selman KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. Ann Neurol. 1988;23:339–346.
14. Okumura A, Mizuguchi M, Kidokoro H, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev. 2009;31:221–227.
15. Köh JC, Murugasu A, Krishnappa J, et al. Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. Pediatr Neurol. 2019;98:80–84.