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Lethal pediatric cerebral vasculitis triggered by Severe Acute Respiratory Syndrome Coronavirus 2: a case report

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Short Title: Cerebral vasculitis from SARS-CoV-2
Abstract:

Objectives: We report the clinical, radiological, laboratory, and neuropathological findings in support of the first diagnosis of lethal, small-vessel cerebral vasculitis triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a pediatric patient.

Patient description: A previously healthy, 8-year-old Hispanic female presented with subacute onset left-sided weakness two weeks after a mild febrile illness. SARS-CoV-2 nasopharyngeal swab was positive. Magnetic resonance imaging (MRI) revealed an enhancing right frontal lobe lesion with significant vasogenic edema. Two brain biopsies of the lesion showed perivascular and intraluminal lymphohistiocytic inflammatory infiltrate consistent with vasculitis. Despite extensive treatment with immunomodulatory therapies targeting primary angiitis of the central nervous system, she experienced neurologic decline and died 93 days after presentation. SARS-CoV-2 testing revealed positive serum IgG and positive cerebrospinal fluid IgM. Comprehensive infectious, rheumatologic, hematologic/oncologic, and genetic evaluation did not identify an alternative etiology. Post-mortem brain autopsy remained consistent with vasculitis.

Discussion: This is the first pediatric presentation to suggest SARS-CoV-2 can lead to a fatal, post-infectious, inflammatory small-vessel cerebral vasculitis. Our case is unique in including supportive cerebrospinal fluid and post-mortem tissue analysis. While most children recover well from neurologic complications of SARS-CoV-2, we emphasize the potential mortality in a child with no risk factors for severe disease.

Keywords: SARS-CoV-2, COVID, vasculitis, pediatrics
Clinical Observation:

Introduction:

We describe the comprehensive evaluation and ultimately fatal course of an 8-year-old girl who presented with left-sided weakness and was found to have a brain lesion. After extensive evaluation the brain lesion was felt to be vasculitis triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The lesion was progressive and refractory to numerous immunotherapies targeting cerebral vasculitis, and the patient unfortunately passed away. This is the first reported pediatric case of lethal small-vessel cerebral vasculitis triggered by SARS-CoV-2, as evidenced by positive cerebrospinal fluid (CSF) SARS-CoV-2 IgM antibodies. Clinicians should be cognizant of the potential mortality of this post-infectious neurologic complication of SARS-CoV-2 in children without medical comorbidities.

Case Presentation:

An 8-year-old previously healthy, fully immunized (excluding vaccination for SARS-CoV-2 which had not yet been developed) Hispanic female presented with left-sided weakness. Two weeks prior, she had several hours of fever, cough, and headache. Her family noticed left foot weakness after a fall, followed by left arm weakness. On presentation she had left-sided arm weakness (4/5 strength), leg weakness (proximal 4/5, distal 0/5 strength), hyperreflexia, ankle hypertonia, and Babinski. Her birth and family history were unremarkable.

Laboratory and Imaging Studies:

SARS-CoV-2 nasopharyngeal PCR test on hospital day one prior to anesthesia for magnetic resonance imaging (MRI) returned positive. MRI of the brain and cervical spine (Figure 1A) demonstrated a right frontal lobe enhancing lesion with vasogenic edema. Incidental encephalomalacia in
the left basal ganglia indicative of remote infarct was noted. Differential diagnosis was tumefactive
demyelination versus tumor.

Due to diagnostic uncertainty, a brain biopsy was performed on hospital day four. Pathology
demonstrated infarct-like necrosis with perivascular lymphohistiocytic inflammatory infiltrates, the
majority being T-lymphocytes (Figure 2A-D). Bacterial, fungal cultures, and viral immunohistochemistry
were negative. Tissue analysis favored vasculitis and excluded neoplasm and demyelination. Extensive
evaluation for infectious, autoimmune, hematologic, oncologic, and genetic etiologies was done
(Supplemental Table 1A and 1B) and was normal except for positive mycoplasma serology which was
considered incidental.

On hospital day nine serum SARS-CoV-2 IgG qualitative testing was positive. Multiple
subsequent nasopharyngeal SARS-CoV-2 PCR tests were negative (Supplemental Table 1D). SARS-
CoV-2 testing of fresh frozen brain biopsy tissue was negative. At time of evaluation there was no
validated CSF SARS-CoV-2 test.

Treatment and Further Evaluation:

Initial suspicion for tumefactive demyelination led to treatment with intravenous (IV)
methylprednisolone followed by plasmapheresis. During plasmapheresis, arm weakness worsened and left
lower face weakness developed. MRI showed enlarged lesion with extension into the corpus callosum
(Figure 1B). Given biopsy concern for vasculitis, cyclophosphamide was administered. Weekly MRI
studies demonstrated progression of the lesion despite all interventions (Figure 1C).

A second brain biopsy was performed to rule out inadequate sampling of neoplasm by the first
biopsy. Pathology showed parenchymal destruction with features of small vessel lymphohistiocytic
vasculitis and no neoplastic cells (Figure 2E-G). A second dose of cyclophosphamide was administered,
followed by rituximab and IV immunoglobulin. Neurologic exam continued to decline.
Sixty-two days after presentation the patient developed headache, status epilepticus, and neurologic exam acutely declined. Imaging revealed expansion of the lesion with midline shift. Levetiracetam, neuroprotective measures for elevated intracranial pressure, and broad-spectrum antimicrobials (including azithromycin, antifungal and parasitic coverage) were initiated. IV methylprednisolone was restarted, and infliximab was given for presumed treatment-resistant vasculitis.

Laboratory testing at that time revealed anemia, leukopenia, thrombocytopenia, and elevated inflammatory markers (Supplemental Table 1C). Persistent fevers developed. Bone marrow biopsy demonstrated hypocellularity, but no hemophagocytosis nor signs of malignancy. Due to fevers, cytopenias, hyperferritinemia, and elevation in liver enzymes, a diagnosis of secondary macrophage activation syndrome was postulated for which she received a course of anakinra for additional immunosuppression and central nervous system (CNS) penetration.

Unrelenting clinical decline and progression of MRI findings (Figure 1D) led to transition to comfort care. The patient passed 93 days after presentation.

Post-mortem Evaluation:

Brain autopsy (Figure 2H) showed a large necrotic region and smaller satellite lesions. Histology revealed diffuse acute hypoxic/ischemic changes along with massive parenchymal infarct, multifocal hemorrhages, and perivascular inflammatory infiltrates confined to areas adjacent to the large areas of infarction. There were scattered small parenchymal infarcts of various ages, which did not appear to show surrounding inflammatory infiltrate. The atypical lymphohistiocytic vessel-associated inflammatory infiltrate had a similar morphology to the prior biopsies, including T-lymphocyte predominance. Non-lesional background brain showed no significant inflammation. Electron microscopy on fragments of brain did not show evidence of viral particles.
Post-mortem, the Center for Disease Control and Prevention tested for SARS-CoV-2 on CSF from hospitalization day two, which returned strongly positive for SARS-CoV-2 IgM (Figure 3). The extensive negative evaluation, lack of evidence on autopsy for an alternative diagnosis, and presence of SARS-CoV-2 IgM in the initial CSF led to the hypothesis that the underlying disease was a reactive inflammatory vasculitis secondary to SARS-CoV-2.

Discussion:

Solitary CNS lesions present a diagnostic challenge. Initial differential diagnoses were high-grade glioma versus tumefactive demyelination, followed by CNS hemophagocytic lymphohistiocytosis, infection, and vasculitis. Acute disseminated encephalomyelitis (ADEM) was not considered due to lack of encephalopathy. Tumefactive demyelinating lesions are rare in children and biopsy is often required for definitive diagnosis. Two brain biopsies excluded neoplasm. The first biopsy revealed extensive necrosis with perivascular inflammation and rare microthrombi, raising the question of vasculitis, which was bolstered by the second biopsy demonstrating dense transmural inflammatory infiltrate. Small-vessel primary angiitis of the CNS in childhood (SV-cPACNS) typically presents with encephalopathy, seizure, ataxia, headache, or neuropsychiatric disturbances. The typical histopathological pattern in SV-cPACNS is predominately intramural/perivascular activated T-cell lymphocytic infiltrate. PACNS can rarely present as a tumor-like lesion in 7% of adults and isolated case reports of children. As viral infections are known to trigger CNS vasculitis, we questioned if SARS-CoV-2 could incite a necrotizing vasculopathy. In this patient, the presence of chronic encephalomalacia in the left basal ganglia was felt to hint she could be at risk for arteriopathies.

SARS-CoV-2 arose in 2019 and has spread globally. In the United States as of July 2021, children under 18 represent 12.6% of cases. Neurologic manifestations of SARS-CoV-2 include stroke,
cerebral venous sinus thrombosis, seizure, meningitis, encephalitis, ADEM, acute fulminant cerebral edema, posterior reversible encephalopathy syndrome, myelitis, Guillain-Barré syndrome, cranial neuropathies, headache, myositis, and weakness⁷⁻⁹.

Children with SARS-CoV-2 and neuroimaging findings are reported to recover well, with exceptions being deaths from fatal co-infections (4 patients), acute fulminant cerebral edema in the setting of status epilepticus (3 patients), stroke (4 patients, one of whom is the patient described in this article), and severe encephalopathy (4 patients)⁷⁻⁹. CNS vasculitis has been reported in adults with SARS-CoV-2¹⁰. In pediatrics, isolated vascular events from focal cerebral arteriopathies have been reported⁸.

It has been postulated that pro-inflammatory cytokines associated with SARS-CoV-2 lead to enhanced permeability of the blood-brain-barrier, allowing antibodies and other pro-inflammatory mediators into the brain parenchyma, perpetuating a post-infectious CNS inflammatory response¹¹.

SARS-CoV-2-related neuropathology findings in the literature are described as either hypoxic/ischemic changes secondary to respiratory/cardiovascular compromise, acute thrombotic ischemic and/or hemorrhagic infarcts within the brain parenchyma, or lesions similar to those seen in ADEM. Rare cases in the adult population have shown focal or diffuse perivascular T-lymphocytic infiltrate¹⁰, similar to what was encountered in our patient¹².

Mycoplasma has been associated with CNS disease including vasculitis, ADEM, Guillain-Barré syndrome and encephalitis mimicking brain mass¹³,¹⁴. A mechanism of vasculitic necrosis associated with Mycoplasma has been proposed; however, this has only been reported in the thalamus, basal ganglia, pons, and splenium of the corpus callosum, which is not consistent with our patient’s presentation, nor is the enlargement of our patient’s lesion after treatment with azithromycin¹⁴.

Although multisystem inflammatory syndrome in children (MIS-C) has arisen during the SARS-CoV-2 pandemic, our patient never met diagnostic criteria due to lack of daily fevers, other additional clinical features consistent with MIS-C, nor significant inflammatory response at time of presentation¹⁵.
Furthermore, symptoms of MIS-C present approximately four weeks from acute SARS-CoV-2 infection; thus MISC-C would not have been considered when fevers and inflammatory markers rose two months after her initial presentation. Instead, these findings were attributed to possible reactive macrophage activation syndrome.

Conclusion:

We suspect our patient’s progressive cerebral infarction was caused by SV-cPACNS, precipitated by an exaggerated immune response to SARS-CoV-2. The time course of preceding illness, positive SARS-CoV-2 testing (nasopharyngeal PCR, serum and plasma IgG, and CSF IgM), and lack of systemic inflammation at presentation are suggestive of a post-infectious mechanism of disease. We believe this is the first pediatric case to suggest SARS-CoV-2 can lead to a fatal, post-infectious, inflammatory CNS vasculitis.

Acknowledgment Section:

We thank the family for allowing us to report this case, and the kindness and graciousness they showed us throughout their child’s illness. Informed consent (written and oral) was obtained from family for this publication. To the inpatient RNs for the wonderful care they gave to the patient. To our medical colleagues in many subspecialities who let us discuss the case with them (particularly Dr. Maureen O’Brien and Dr. Alexei Grom), and to our colleagues at outside institutions who provided second opinions on imaging and pathology results. Finally, we are very grateful to Natalie J. Thornburg, PhD and her team at the Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, the Center for Disease Control and Prevention, for testing our patient’s lab samples and sharing the results with us, including Figure 3.

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Previous Presentation of the information in this manuscript: Our patient was included in very limited detail in the study “Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome”, published in JAMA Neurology in March 2021. In that study’s text our patient is the fourth stroke patient who died, and her course is summarized in one sentence within the body of the manuscript. In supplemental e-Table 4 she is presented as Case 3. The authors of that study had limited access to data, and no access to imaging on our patient, and their manuscript was published before our patient’s post-mortem autopsy was performed and the CSF SARS-CoV-2 IgM result was known.

References:


**Tables and Figures:**

**Figure 1:** Imaging findings. (A) Axial T1-weighted MR image with contrast through the frontal lobes shows an enhancing lesion with diffusion restriction centered in the right corona radiata, including extension into the precentral gyrus, with extensive surrounding edema. The cortical component had hemorrhagic staining. Exam performed 2 weeks later (B) shows increased size of the enhancing component, with central non-enhancement. (C) Contrast-enhanced image 6 weeks after presentation demonstrates further progression of the lesion, with enhancement extending throughout much of the entire cerebral hemisphere. (D) 10 weeks after presentation the lesion had spread throughout the right hemisphere, with substantial extension across the corpus callosum into the left hemisphere, with non-contiguous peripheral lesions apparent (arrow).

**Figure 2:** Brain biopsies and autopsy findings. A-D) Initial biopsy: A) Relatively bland ischemic necrosis with cellular loss of nuclear basophilia along with perivascular inflammation. B) Patchy areas of intraparenchymal inflammation and gliosis. C) CD3 (brown) and CD20 (red) dual chromogen immunohistochemistry revealing predominance of CD3 positive T-lymphocytes in the vascular walls and perivascular infiltrates. D) CD163 highlights vascular and intraparenchymal histiocytes. E-G) Second Biopsy: E) Similar findings to previous biopsy including transmural and perivascular inflammation, but also with areas of cystic change and foamy histiocytes (right upper corner). F) CD163 highlighting histiocytes. G) CD3 highlighting T-lymphocytes. H) Coronal section of brain at autopsy revealing confluent areas of necrosis from cortex to corpus callosum and basal ganglia, hemorrhage near previous biopsy. Microscopic images are 400x magnification.

**Figure 3:** CSF SARS-CoV-2 testing. CSF testing showing strong SARS-CoV-2 IgM positivity on left, and negative SARS-CoV-2 IgG on right.

Supplemental Table 1A, 1B, 1C, 1D: Supplementary Laboratory and Imaging Results
Figure 1. (A) Axial T1-weighted MR image with contrast through the frontal lobes shows an enhancing lesion with diffusion restriction centered in the right corona radiata, including extension into the precentral gyrus, with extensive surrounding edema. The cortical component had hemorrhagic staining. Exam performed 2 weeks later (B) shows increased size of the enhancing component, with central non-enhancement. (C) Contrast-enhanced image 6 weeks after presentation demonstrates further progression of the lesion, with enhancement extending throughout much of the entire cerebral hemisphere. (D) 10 weeks after presentation the lesion had spread throughout the right hemisphere, with substantial extension across the corpus callosum into the left hemisphere, with non-contiguous peripheral lesions apparent (arrow).
Highlights:

- Some people with SARS-CoV-2 can have a post-infectious inflammatory reaction
- SARS-CoV-2 can cause small-vessel cerebral vasculitis in children
- Vasculitis can be resistant to immunomodulatory therapies, leading to death
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