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Case Report

Neuropsychiatric Symptoms in an Adolescent Boy With Multisystem Inflammatory Syndrome in Children

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Introduction

The recent SARS-CoV-2 pandemic has been associated with emergence of a new syndrome referred to as multisystem inflammatory syndrome in children (MIS-C) related to coronavirus disease-2019 (COVID-19). As this is an emerging syndrome, knowledge of its presentation and pathophysiology is evolving. MIS-C is currently defined by the presence of fever, inflammation, and multiorgan dysfunction in the context of present or recent SARS-CoV-2 infection or known COVID-19 exposure.[1] The syndrome has similarities to Kawasaki disease (KD) and toxic shock syndrome. Case series of Europe and the United States have described presenting symptoms variably including fever, gastrointestinal symptoms, rash, mucosal changes, adenopathy, edema, and respiratory symptoms.[2–11] Headache, irritability, and confusion have also been described, but details regarding these neuropsychiatric symptoms have not been provided. Given the paucity of knowledge concerning this syndrome's effect on the nervous system, the intent of this case report is to describe the neuropsychiatric symptoms in a 14-year-old boy presenting with multisystem inflammatory syndrome and positive SARS-CoV-2 antibodies.

Case

A 14-year-old African-American boy, with no past medical or psychiatric history, presented to an emergency department in New York City with abdominal pain, fever, and truncal rash in mid-May, 2020. He had no known sick contacts, and no members of his family had been diagnosed with COVID-19. In the emergency department, he was found to have a painful, distended abdomen and was febrile to 102.8°F with tachycardia and hypotension concerning for shock. Laboratory studies were notable for low white blood cell count (3.8 k/μL) and elevations in C-reactive protein (30.2 mg/dL), creatinine (1.4 mg/dL), erythrocyte sedimentation rate (53 mm/h), ferritin (1305 ng/mL), D-dimer (>20 μg/mL), bilirubin (2.2 mg/dL), and liver enzymes (alanine aminotransferase 31 U/L, aspartate aminotransferase 53 U/L). SARS-CoV-2 polymerase chain reaction (PCR) testing was negative. Chest and abdominal computed topography showed diffuse enterocolitis and bilateral ground glass opacities in the lungs. He received fluid resuscitation, empiric antibiotics, and a surgical evaluation. He was admitted to the pediatric intensive care unit where he required initiation of norepinephrine to support falling blood pressure. Arterial and central venous catheters were inserted using brief sedation with ketamine and midazolam.

On the day of admission, he was started on a 5-day course of methylprednisolone 0.5 mg/kg every 6 hours, as well as anticoagulation with low-molecular-weight heparin. He was placed on high-flow nasal cannula for worsening respiratory distress and was

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noted to have peripheral and facial edema, likely secondary to fluid resuscitation. Serum interleukin-6 was significantly elevated at 5651 pg/mL (normal < 17.4 pg/mL), whereas interleukin-1 was mildly elevated at 3.4 pg/mL (normal < 3.0 pg/mL). Echocardiogram showed a left ventricular ejection fraction of 58% and mild coronary artery dilation (z-score < 2.5). During the first night of hospitalization, he was noted to be restless, agitated, and confused. Soft wrist restraints were temporarily applied after he pulled out his femoral central line and nasogastric tube. Ketamine was administered for replacement of the central line, and a dexmedetomidine drip was started to reduce agitation.

On the second hospital day, his parents felt that he was back to his usual self, though sleepy. Owing to concerns for worsening cytokine storm, he received a single dose of anakinra to target the multisystem inflammation. A repeat echocardiogram showed worsening left ventricular function (ejection fraction 42%), and milrinone was started. Repeat SARS-CoV-2 PCR testing was again negative. As the day progressed, he again became disoriented and confused, intermittently sleeping for 10–15 minutes at a time, then awakening, and attempting to leave the bed. This culminated in an episode of agitation in the early afternoon during which he was disoriented, appeared to respond to internal stimuli, and became aggressive. Several staff members were required to physically restrain him to prevent injury, and haloperidol 5 mg was given intravenously (IV) to target psychosis. Haloperidol was perceived to worsen the agitation, so 20 minutes later, lorazepam 2 mg IV was administered, after which he calmed and fell asleep. The child and adolescent psychiatry team was consulted but were unable to perform a full evaluation owing to medication effects. The psychiatry team suspected hyperactive delirium because of the fluctuating changes in awareness and attention, though the reported worsening of agitation with haloperidol and improvement with lorazepam raised concern for possible agitated catatonia. With this differential in mind, the team recommended olanzapine 5 mg by mouth at bedtime. The dexmedetomidine drip was also increased. By that afternoon, he had met diagnostic criteria for atypical KD, so a course of 2 g/kg of IV immunoglobulin was initiated, divided over 4 days because of concerns for excess fluid volume in a patient with diminished ventricular heart function and persistent tachypnea.

On hospital day 3, he remained sedated on dexmedetomidine with intermittent restlessness and verbal aggression inconsistent with his baseline character, which was described as quiet and shy. On hospital day 4, the dexmedetomidine drip was discontinued, and immediately, he demonstrated confusion, disorientation, delusions, and aggression. He again received lorazepam 2 mg IV, which had a calming effect, and dexmedetomidine was restarted. He was given an additional dose of olanzapine 5 mg by mouth for refractory delirium, and the standing dose was increased to 5 mg twice a day. A noncontrast magnetic resonance imaging study of the brain was obtained and was unremarkable. A lumbar puncture was considered but not performed owing to his anticoagulation status. Laboratory studies showed ferritin at its peak (1753 ng/mL), whereas d-dimer declined for the first time to 13.37 μg/mL, and C-reactive protein (which peaked on day of admission) had come down to 7.8 mg/dL.

On hospital day 5, the dexmedetomidine drip was once again discontinued, this time without emergent agitation. The pediatric neurology team evaluated him and found him to be sleepy, inattentive, and unable to follow multistep commands. Tone, strength, and sensation were all intact.

Over hospital days 6–8, he showed gradual improvements. He was able to wean off norepinephrine and milrinone, markers of kidney and liver injury improved, and inflammatory markers continued to come down. Coronavirus antibody testing showed presence of SARS-CoV-2 immunoglobulin G antibodies. The olanzapine was decreased from twice a day to once a day and then discontinued. Ongoing abnormalities in mental status documented by pediatric intensive care unit staff included increased speech latency, flat affect, and minimal spontaneous activity.

By hospital day 9, he was stable on room air. He had been off antipsychotics for over 24 hours and had not had recurrence of agitation. This was the first occasion when the psychiatry team was able to perform a formal, in-person mental status examination while he was awake. The examination was significant for flat affect, poor eye contact, and minimal spontaneous movement or speech. His thought process was concrete but linear. On cognitive assessment, he was oriented to self, date, and location (hospital) but not circumstances. He believed that he was still in the emergency department and was unaware of how long he had been in the hospital. He had significant impairment in attention,

concentration, and short-term memory demonstrated by inability to perform serial 7s (became stuck after first subtraction) or serial 3s (adding instead of subtracting, despite several prompts), inability to say days of the week backwards (reversed directions after 2 d), and difficulty recalling events from earlier in the day. Strength and tone were normal, but he showed slowing on rapid alternating movements. He was able to follow simple commands ("Touch my finger") but not multistep commands ("Touch my finger then touch your ear"). He had no difficulty repeating sentences ("No ifs, ands, or buts"), but he demonstrated impairments in executive functioning on the clock-drawing task, needing to have instructions reiterated repeatedly and initially writing all the numbers on one side. He positioned the clock hands to show 6:00 rather than the time instructed (2:50). There was no evidence of hallucinations, delusions, or waxing and waning of his mental status on examination.

As of hospital day 11, he appeared to be back to his baseline neurocognitive status as per his parents' assessment: that of a typically developing 8th grader. On mental status examination, spontaneous movement and speech had returned, and affect was reactive and appropriate. He exhibited good eye contact, full cooperation, and ability to follow complex multistep commands ("Touch my finger, then touch your ear and close your eyes"). Attention, concentration, and short-term memory were all improved as demonstrated by ability to complete serial 7s without hesitation, successfully spelling WORLD backwards, and detailed recall of recent events and conversations. Repeat inflammatory markers showed interleukin-6 49 pg/mL, ferritin 584 ng/mL, D-dimer 2 μg/mL, C-reactive protein 5 mg/dL. He was discharged home the following day.

Discussion

MIS-C is a systemic inflammatory syndrome that presents similarly, though not identically, to KD, an inflammatory syndrome associated with systemic vasculitis.[12] Classic KD presents with fever in combination with rash, cervical lymphadenopathy, conjunctivitis, mucosal changes, and swelling/redness of the extremities.[13] Most cases of MIS-C reported thus far have not met full criteria for KD, but overlapping symptoms have been present to varying degrees.[11] Based on review of 10 case series published so far, fever is the most prevalent presenting symptom (part of the case definition), followed by gastrointestinal complaints (present in 60–100% of cases). Rates of neurological and/or neuropsychiatric symptoms have ranged from 25% to 56% with the most common symptom being meningism, followed by headache and irritability. Confusion has been reported less frequently, but the exact incidence is unclear owing to lumping with other neurological symptoms.[2–11] Five of the 10 case series reviewed specifically mentioned confusion as a presenting symptom in at least one of the included patients.[4–6,9,11] Overt delirium and/or neurocognitive changes have not been specifically reported.

The relationship between MIS-C and SARS-CoV-2 remains undetermined. An epidemiological study of MIS-C in France demonstrated that cases of MIS-C peaked approximately 4–6 weeks after the peak of COVID-19 cases in that country.[14] This finding suggests a postinfectious inflammatory process, though the temporal relationship with the virus is still under investigation. Across case series, the number of patients with MIS-C who had a positive SARS-CoV-2 PCR ranged from 13% to 69%, whereas the number of patients with positive serology ranged from 53% to 97%.[2–11] Some of the discrepancy across and within studies is due to changes in the availability of these tests over time. Our patient's positive antibodies with negative PCR supports the postinfectious theory, though the finding of ground glass opacities on chest computed topography raised concern for active infection.

Initial neuropsychiatric symptoms in our patient included fluctuating impairment in awareness and attention with psychosis and agitation consistent with acute hyperactive delirium. The apparent worsening of symptoms with administration of haloperidol and unexpected improvement with lorazepam (which often worsens delirium symptoms) could suggest involvement of the N-methyl-D-aspartate and/or γ-aminobutyric acid pathways in his symptomatology, but we are reluctant to speculate based on this single observation. Confounding variables for worsening agitation include physical restraint and crowding by staff. Delirium was followed by persistent paucity of spontaneous movement and speech (once symptoms were no longer waxing/waning) and persistent impairment in executive functioning including attention, memory, and planning. All of these symptoms gradually resolved as the underlying illness improved. Use of a formal

neurocognitive assessment tool such as the Mini-Mental Status Exam or Montreal Cognitive Assessment may have provided richer detail about the trajectory of the cognitive impairment, but these tools are not routinely used by our child and adolescent psychiatry service owing to lack of established validity in pediatric patients. One study has shown validity of the Montreal Cognitive Assessment in assessment of cognitive symptoms in adolescents with congenital heart disease, but research in broader pediatric populations is needed.[15]

Because MIS-C most closely resembles KD, our experience with neuropsychiatric symptoms in KD can serve as a comparison. Although neuropsychiatric symptoms are not considered hallmarks of KD, there have been case reports of neurological complications ranging from encephalitis to focal neurological symptoms. Specifically, Terasawa et al.[16] published a case series of neurological complications in KD where they described 6 cases: 4 cases with facial nerve palsy, 1 with hemiplegia, and a final patient had both facial palsy and hemiplegia. Cases with more diffuse central nervous system involvement include one describing a 4-year-old patient with hypotonia, coma, hemiparesis, and seizures during the acute phase of KD illness followed by prolonged neurocognitive impairment resembling autism with intractable seizures.[17] Another case series described 4 patients with the syndrome of mild encephalopathy with a reversible splenial lesion in the context of KD. The clinical symptoms in these patients included delirium and drowsiness lasting 3–8 days with normal cerebral spinal fluid studies and characteristic findings on magnetic resonance imaging.[18] Finally, a team in Serbia described a 7-year-old boy who presented with generalized convulsive status epilepticus and depressed mental status thatwas attributed to cerebral vasculitis secondary to KD. His symptoms improved significantly with IV immunoglobulin and steroid treatment.[19]

There are several potential mechanisms for our patient's neuropsychiatric symptoms, and the etiology was almost certainly multifactorial. First, delirium and other neuropsychiatric symptoms ranging from encephalitis to focal neuropathies, changes in taste and smell, and acute brainstem dysfunction have been described in patients with COVID-19.[20,21] The relationship between the SARS-CoV-2 virus and these neurological manifestations may be primary, secondary, or both. A portion of the neuropsychiatric manifestations are likely due to secondary mechanisms such as hypoxia, systemic inflammation, and coagulopathy, but cerebral spinal fluid studies and pathological analysis of brain tissue in some patients have shown evidence for direct neurotropic activity by the virus.[22] Although our patient's SARS-CoV-2 PCR testing was negative, we cannot rule out active infection.

Cytokine neurotoxicity is also high on the differential as elevated interleukin-6 has been independently linked to delirium in adults.[23,24] Cytokine storm has been documented in COVID-19 infections, and cytokines are similarly thought to play an important pathologic role in KD.[13,25] Knowledge of the neurotoxicity of cytokines is primarily derived from experience with T cell therapies, which are known to trigger cytokine release syndrome. This cytokine release has been associated with confusion, delirium, and language disturbances.[26] Neurotoxicity from cytokines would explain why our patient manifested the most severe symptoms during the period when his inflammatory markers were most elevated.

Another potential explanation is direct involvement of the central nervous system by autoantibodies. Autoantibodies targeting the central nervous system in the postinfectious period has been documented in syndromes including acute disseminated encephalomyelitis and autoimmune encephalitis.[27] Because no lumbar puncture was performed, it was not possible to directly evaluate the cerebral spinal fluid for evidence of a humoral immune process, which could include presence of white blood cells, elevated proteins, or oligoclonal bands. Our patient's unremarkable magnetic resonance imaging is inconclusive given that magnetic resonance imagings are often normal in autoimmune encephalitides, especially in the early phases of illness.[28] The effectiveness of IV immunoglobulin in the treatment of MIS-C suggests that antibodies likely play a role in the pathophysiology, though as in KD, the exact role of antibodies is yet unknown.[29]

Finally, the neuropsychiatric symptoms could have been secondary to treatment with high-dose corticosteroids. Corticosteroids carry significant risk of neuropsychiatric side effects including mood changes, psychosis, delirium, and changes in executive functioning.[30] Our patient's symptoms began approximately 18 hours after methylprednisolone was initiated and significantly improved after its discontinuation. Because steroid exposure and the peak of the inflammatory process were temporally correlated, it remains

difficult to tease apart their individual effects. Iatrogenic administration of other deliriogenic medications including ketamine, midazolam, and lorazepam may also have contributed to symptoms, though our patient's exposure to these medications was sporadic and failed to temporally associate with symptoms.

Conclusion

As the SARS-CoV-2 pandemic progresses, cases of MIS-C associated with COVID-19 are expected to increase and with it our understanding of the underlying pathophysiology and potential manifestations. There are not, as of yet, any evidence-based treatment guidelines, and owing to the potentially serious outcomes of the presenting syndrome (shock, cytokine storm, vasculitis), early treatment with potent pharmacologic agents is empirically initiated. This case represents one example of neuropsychiatric symptoms associated with MIS-C, but it is not the only one in which similar symptoms were reported. As additional cases are described, a pattern of neuropsychiatric manifestations may emerge, or evidence of an iatrogenic mechanism may become apparent. Hopefully, additional experience and research will provide a better understanding of this syndrome and more targeted interventions.

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References

1. Centers for Disease Control and Prevention: Multisystem inflammatory syndrome in children (MIS-C) associated with Coronavirus disease 2019 (COVID-19). May 14, 2020. Available from: https://emergency.cdc.gov/han/2020/han00432.asp
2. Belhadjer Z, Méot M, Bajolle F, et al: Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.048360
3. Cheung EW, Zachariah P, Gorelik M, et al: Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York city. JAMA 2020:e2010374
4. Chiotos K, Bassiri H, Behrens EM, et al: Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. J Pediatr Infect Dis Soc 2020:piaa069
5. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis: Gastrointestinal symptoms as a major presentation of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. Gastroenterology 2020. https://doi.org/10.1053/j.gastro.2020.05.079
6. Ramcharan T, Nolan O, Lai CY, et al: Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol 2020. https://doi.org/10.1007/s00246-020-02391-2
7. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P: Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395:1607–1608
8. Pouletty M, Borocco C, Ouldali N, et al: Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicenter cohort. Ann Rheum Dis 2020. https://doi.org/10.1136/annrheumdis-2020-217960
9. Toubiana J, Poirault C, Corsia A, et al: Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020; 369:m2094
10. Verdoni L, Mazza A, Gervasoni A, et al: An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395:1771–1778
11. Whittaker E, Bamford A, Kenny J, et al: Clinical characteristics of 58 children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020:e2010369
12. Rauf A, Vijayan A, John ST, Krishnan R, Latheef A: Multisystem inflammatory syndrome with features of atypical Kawasaki disease during COVID-19 Pandemic. Indian J Pediatr 2020. https://doi.org/10.1007/s12098-020-03357-1.
13. Dietz SM, van Stijn D, Burgner D, et al: Dissecting Kawasaki disease: a state-of-the-art review. Eur J Pediatr 2017; 176:995–1009
14. Belot A, Antona D, Renolleau S, et al: SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill 2020; 25:2001010
15. Pike NA, Poulsen MK, Woo MA: Validity of the Montreal cognitive assessment screener in adolescents and young adults with and without congenital heart disease. Nurs Res 2017; 66:222–230.
16. Terasawa K, Ichinose E, Matsuishi T, Kato H: Neurological complications in Kawasaki disease. Brain Dev 1983; 5:371–374

17. Tobarki B, Mahdhaoui A, Selmi H, Yacoub M, Essoussi AS: Kawasaki disease with predominant central nervous system involvement. Pediatr Neurol 2001; 25:239–241
18. Takanashi J, Shirai K, Sugawara Y, Okamoto Y, Obonai T, Terada H: Kawasaki disease complicated by mild encephalopathy with a reversible splenial lesion (MERS). J Neurol Sci 2012; 315:167–169
19. Stojanovic VD, Radovanovic TD, Koprivsek KM, Vijatov Duric GV, Dronjski AD: Kawasaki disease complicated with cerebral vasculitis and severe encephalitis. Ann Indian Acad Neurol 2020; 23:228–232
20. Li H, Xue Q, Xu X: Involvement of the nervous system in SARS-CoV-2 infection. Neurotox Res 2020; 38:1–7
21. Rogers JP, Chesney E, Oliver D, et al: Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7:611–627
22. Zhou Z, Kang H, Li S, Zhao X: Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 2020:1–6
23. McNeil JB, Hughes CG, Girard T, et al: Plasma biomarkers of inflammation, coagulation, and brain injury as predictors of delirium duration in older hospitalized patients. PLoS One 2019; 14:e0226412
24. Chen Y, Lu S, Wu Y, et al: Change in serum level of interleukin 6 and delirium after coronary artery bypass graft. Am J Crit Care 2019; 28:462–470
25. McGonagle D, Sharif K, O'Regan A, Bridgewood C: The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020; 19:102537
26. Gust J, Taraseviciute A, Turtle CJ: Neurotoxicity associated with CD19-targeted CAR-T cell therapies. CNS Drugs 2018; 12:1091–1101
27. Sonneville R, Klein I, de Broucker T, Wolff M: Post infectious encephalitis in adults: diagnosis and management. J Infect 2009; 58:321–328
28. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B: Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis. AJNR Am J Neuroradiol 2017; 38:1070–1078
29. Lindquist ME, Hicar MD: B cells and antibodies in Kawasaki disease. Int J Mol Sci 2019; 20:1834
30. Bhangle SD, Kramer N, Rosenstein ED: Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychiatric lupus. Rhematol Int 2013; 33:1923–1932