Abstract: Multisystem inflammatory syndrome in children (MIS-C) is a rare but life-threatening inflammatory immune response associated with severe acute respiratory syndrome coronavirus 2 infection. The majority of patients have been presented with hypotension, shock, gastrointestinal, cardiovascular and mucocutaneous symptoms. The incidence of neurologic symptoms in MIS-C is of rising concern as they are not well described and reported in fewer patients. An 8-year-old boy was admitted to the hospital with headache, fever, conjunctivitis, and hyperinflammatory findings diagnosed as MIS-C. Fundus examination performed with complaints of headache, vomiting, and conjunctivitis showed bilateral papilledema. Pseudotumor cerebri is a rare manifestation of MIS-C that can lead to vision loss and may not only be resolved with the standard treatment for MIS-C. We report a case of MIS-C presented with neurologic symptoms due to pseudotumor cerebri and successfully treated with intravenous immunoglobulin and acetazolamide.

Keywords: MIS-C, papilledema, SARS-CoV-2, pseudotumor cerebri

The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in China at the end of 2019. Subsequently, SARS-CoV-2 spread worldwide, and the World Health Organization (WHO) declared a pandemic on March 11, 2020. SARS-CoV-2 infection is generally asymptomatic or mildly symptomatic in children, and mortality rates are lower than in adults. At the end of April 2020, the Pediatric Intensive Care Society (PICS) reported cases with hyperinflammatory findings and severe multisystemic inflammation similar to Kawasaki disease and toxic shock syndrome. This new syndrome is named multisystem inflammatory syndrome in children (MIS-C). It is a rare but life-threatening inflammatory immune response associated with SARS-CoV-2 infection. Centers for Disease Control and Prevention (CDC), WHO and Royal College of Pediatrics and Child Health defined diagnostic criteria for MIS-C. The main aspects of diagnosis are persistent fever, symptoms of two or more organ dysfunction, laboratory evidence of inflammation, lack of alternative diagnosis and evidence of recent or current SARS-CoV-2 infection or exposure. The majority of patients have been presented with hypotension, shock, gastrointestinal, cardiovascular and mucocutaneous symptoms. The incidence of neurologic symptoms in MIS-C was 13%–21% of patients, and they are not well described. Headache, altered mental status, seizures, brain edema, encephalopathy, aseptic meningitis and intracranial hypertension are some of the reported neurologic findings. Therefore, we report a case of MIS-C presented with neurologic symptoms due to pseudotumor cerebri (PTC).

CASE PRESENTATION

A previously healthy 8-year-old boy was admitted to the emergency room with a high fever and fatigue history for 7 days of the duration. He was initially managed as an upper respiratory tract infection but readmitted to the emergency room after 3 days because of persistent fever, headache, vomiting, abdominal pain, redness and swelling in both eyes. His father had a history of SARS-CoV-2 infection 1 month ago, but the patient was not tested for SARS-CoV-2. On admission, his physical examination revealed a fever (38.1°C) and tachycardia (heart rate, 130/min). He had bilateral nonpurulent conjunctivitis. On neurologic examination, his mental status and cranial nerve examination were normal, bilateral papilledema was detected by fundus examination. Detailed ophthalmologic examination showed stage 3 papilledema, and visual functions were as follows: visual acuity as a counting finger from 4 meters, and minimal enlargement of the blind spot. Initial laboratory results were as follows: total leukocyte count: 15.3 × 10^9/L (neutrophil 64.8%, monocyte 4.9 % and lymphocyte 22.9%), hemoglobin 9.7 g/dL, platelet count: 506 × 10^3/μL, C-reactive protein 14.6 mg/dL, and CRP 15.3 mg/L. The Pediatric Infectious Disease Journal • Volume 40, Number 12, December 2021

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| Case report | Age, sex | Systemic symptoms | Neurologic symptoms | Fundus examination | LP | Neuroimaging | Treatment | Outcome |
|-------------|----------|-------------------|-------------------|-------------------|----|-------------|----------|---------|
| Verkuil et al | 14 y/o Female | Fever, Abdominal pain | Headache, Diplopia | No papilledema | WBC: 0 | MRE, MR venography, normal | IVIG, IVMP, Hydrocortisone | Discharged with clinical symptoms resolved 5 months later |
| Baccarella et al | 9 y/o Male | Fever, Abdominal pain | Headache, Diplopia | Bilateral papilledema | WBC: 0 | CT, normal | IVIG, MR venography, normal | Papilledema resolved 2 months later |
| Becker et al | 6 y/o Male | Fever, Abdominal pain | Headache, Diplopia | Bilateral papilledema | WBC: 4 | MRE, MR venography, normal | IVIG, IVMP, Hydrocortisone, Aspirin | Papilledema resolved 2 months later |
| Bilen et al | 13 y/o Female | Fever, Abdominal pain | Headache, Diplopia | Bilateral papilledema | WBC: 218, 90% neutrophils | CT, normal | IVIG, IVMP, Hydrocortisone, Aspirin | Papilledema resolved 5 months later |
| Current case | 8 y/o Male | Fever, Abdominal pain | Headache, Diplopia | Bilateral papilledema | WBC: 0 | MRE, CT, normal | IVIG, IVMP, Hydrocortisone, Aspirin | Papilledema resolved 1.5 months later |

CT indicates computed tomography; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; OP, opening pressure; H2O, water; WBC, white blood cell.
raphy was normal. Lumbar puncture (LP) demonstrated a normal space, vertical tortuosity of the optic nerve (Fig. 1) and MR venography enlargement of the perioptic nerve. CSF magnetic resonance imaging (MRI) showed signs of intracranial hypertension, as our patient, suggesting that increased intracranial pressure may be an etiologic reason for neurologic symptoms of MIS-C. Dufort et al reported headache, altered mental status and nuchal rigidity at presentation, as our patient, indicating that increased intracranial pressure can be within expected ranges. In these cases, the opening pressure can be within expected ranges. In some cases, like our case, LP examination except for abducens palsy, normal MRI findings and pseudotumor cerebri syndrome are papilledema, all of their patients had neurologic symptoms. Diagnostic criteria for definite pseudotumor cerebri syndrome are papilledema, regular neurologic symptoms and confusion as neurologic symptoms. The diagnosis is considered probable pseudotumor cerebri. Neurologic disorders such as systemic lupus erythematosus and Kawasaki disease may present with increased intracranial pressure. In these cases, the diagnosis is considered probable pseudotumor cerebri. Becker et al presented 4 cases of MIS-C with clinical, LP, and neuroimaging findings of increased intracranial pressure, and one of them had papilledema. Baccarella et al also reported two MIS-C cases with symptoms of increased intracranial pressure and papilledema, all of their patients had neurologic symptoms including headache, altered mental status and nuchal rigidity at presentation, as our patient, suggesting that increased intracranial pressure may be an etiologic reason for neurologic symptoms of MIS-C. A review of the MIS-C cases with increased intracranial pressure in the literature is presented in Table 1.

In contrast, in pseudotumor cerebri, our patient was well and hemodynamically stable. It made it easier to perform an LP which did not reveal any significant results. The patient’s headache resolved, and his vision improved after LP, but papilledema was not entirely resolved. We treated the patient with acetazolamide for his papilledema. The hyperinflammatory process was resolved with IVIG in our patient, and visual functions improved on the second day. His papilledema completely regressed on follow-up. Steroids may be reserved for patients without a rapid improvement in visual functions. Fundus examination should be performed in MIS-C patients, mainly showing symptoms compatible with pseudotumor cerebri syndrome. Papilledema is a rare manifestation of MIS-C that can lead to vision loss and may be resolved with standard anti-inflammatory treatment for MIS-C and acetazolamide.

In conclusion, PTC should be kept in mind in MIS-C patients with neurologic symptoms, and treatment should be started immediately to prevent vision loss even in mild cases of MIS-C.

**REFERENCES**

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2020. Available at https://covid19.who.int. Accessed April 2021.
2. Mehta NS, Mytton OT, Mullins EWS, et al. SARS-CoV-2 (COVID-19): what do we know about children? A systematic review. *Clin Infect Dis*. 2020;71:2469–2479.
3. Pediatric Critical Care Society. PICS Statement regarding novel presentation of multisystem inflammatory disease. 2020. Available at https://pccsociety.uk/news/pics-statement-regarding-novel-presentation-of-multisystem-inflammatory-disease/. Accessed April 2021.
4. Becker AE, Chiotos K, McGuire JL, et al. Intracranial hypertension in multisystem inflammatory syndrome in children (MIS-C). *J Pediatr*. 2021;233:263–267.
5. Centers for Disease Control and Prevention (CDC). Multisystem Inflammatory Syndrome in Children. 2020. Available at https://www.cdc.gov/mis-c/chp/. Accessed April 2021.
6. Royal College of Paediatrics and Child Health (RCPCH). Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians. 2020. Available at https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance. Accessed April 2021.
7. Rada T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev*. 2021;38:51–57.
8. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2: a systematic review. *J Pediatr*. 2020;226:45–54.e1.
9. Dufort EM, Kourounis EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med*. 2020;383:347–358.
10. Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. *Neurosci Lett*. 2021;743:135567.
11. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334–346.
12. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health*. 2021;5:323–331.
13. Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC, et al. Multisystem inflammatory syndrome in children: an international survey. *Pediatrics*. 2021;147:e2020024554.

14. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11:995–998.

15. Collantes MEV, Espiritu AI, Sy MCC, et al. Neurological manifestations in COVID-19 infection: a systematic review and meta-analysis. *Can J Neurol Sci*. 2021;48:66–76.

16. Nopp S, Janata-Schwatzek K, Prosch H, et al. Pulmonary embolism during the COVID-19 pandemic: decline in diagnostic procedures and incidence at a university hospital. *Res Pract Thromb Haemost*. 2020;4:835–841.

17. Schupper AJ, Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nerv Syst*. 2020;36:1579–1580.

18. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children [published online ahead of print, 2020 July 1] [published correction appears in JAMA Neurol. 2020 Dec 1;77(12):1582]. *JAMA Neurol*. 2020;77:1–6.

19. Heidary G. Pediatric papilledema: review and a clinical care algorithm. *Int Ophthalmol Clin*. 2018;58:1–9.

20. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81:1159–1165.

21. Leonard EG, Berenson F, Wojtowicz JA, et al. Pseudotumor cerebri associated with kawasaki disease. *J Clin Rheumatol*. 1997;3:310.

22. Katsuyama E, Sada KE, Tatebe N, et al. Bilateral Abducens nerve palsy due to idiopathic intracranial hypertension as an initial manifestation of systemic lupus erythematosus. *Intern Med*. 2016;55:991–994.

23. Baccarella A, Linder A, Spencer R, et al. Increased intracranial pressure in the setting of multisystem inflammatory syndrome in children, associated with COVID-19. *Pediatr Neurol*. 2021;115:48–49.

24. Verkuil LD, Liu GT, Brahma VL, et al. Pseudotumor cerebri syndrome associated with MIS-C: a case report. *Lancet*. 2020;396:532.