Multisystem Inflammatory Syndrome in Children Presenting With Pseudotumor Cerebri and a Review of the Literature

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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

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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[1] SARS-CoV-2 infection is generally asymptomatic or mildly symptomatic in children, and mortality rates are lower than in adults.[2] 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.[3] 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.[4] Centers for Disease Control and Prevention (CDC), WHO and Royal College of Pediatrics and Child Health defined diagnostic criteria for MIS-C.[1,5,6] 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.[1,5,6] 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.[7–9] Headache, altered mental status, seizures, brain edema, encephalopathy, aseptic meningitis and intracranial hypertension are some of the reported neurologic findings.[4,9,10] 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 × 10^3/μL (neutrophil 64.8%, monocyte 4.9 % and lymphocyte 22.9%), hemoglobin 9.7 g/dL, platelet count: 506 × 10^3/μL, C-reactive protein

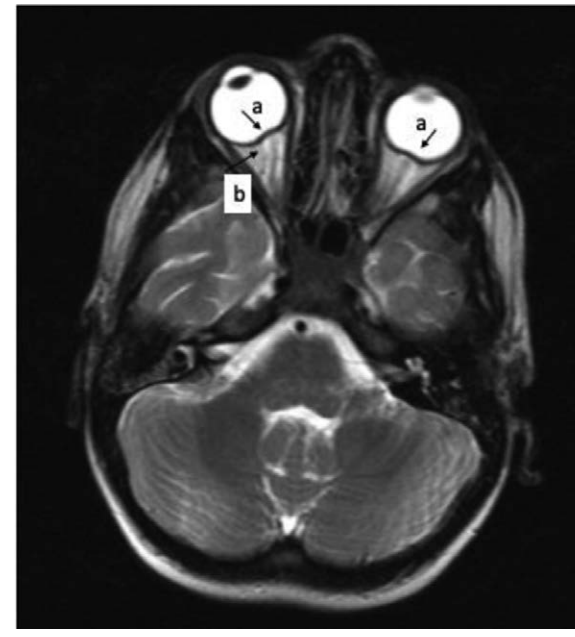

FIGURE 1. Brain magnetic resonance imaging scan showed signs of intracranial hypertension: (a) flattening of the posterior sclera, (b) distention of the perioptic nerve subarachnoid cerebrospinal fluid space, vertical tortuosity of the optic nerve.

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TABLE 1. Review of the MIS-C Cases With Increased Intracranial Pressure in Literature

		Clinical Progression						
Case report	Age, sex	Systemic symptoms	Neurologic symptoms	Fundus examination	LP	Neuroimaging	Treatment	Outcome
Verkuil et al[24]	14 y/o Female	Fever Rash Diarrhea Dyspnea	Headache Abducens palsy	Bilateral Papilledema	OP: 36 cm H_2O WBC: 2 RBC: 0 Glucose: N Protein: N	MRI: eversion of the right optic disc and flattening of the posterior right globe MR venography: normal	IVIG IVMP Antibiotics Hydrocortisone Acetazolamide	Discharged after 14 days resolution of papilledema and abducens palsy
Baccarella et al[23]	9 y/o Male	Fever Abdominal pain	Headache Diplopia	No papilledema	OP: 34 cm H_2O WBC: 0 RBC: 0 Glucose: N Protein: N	MRI: Normal MR Venography: normal	IVIG IVMP Antibiotics Hydrocortisone Acetazolamide Aspirin LMWH	Discharged with clinical symptoms and papilledema resolved
	6 y/o Male	Fever Hypotension, shock	Diplopia Abducens palsy	Bilateral papilledema	OP: 14 cm H_2O WBC: 0 RBC: 0 Glucose: N Protein: N	MRI: kinking and distention of both optic nerve sheaths with protrusion of the optic discs into the globes	IVIG IVMP Antibiotics Hydrocortisone Acetazolamide Aspirin LMWH	Discharged with clinical symptoms resolved Papilledema resolved 5 months later
Becker et al[4]	14 y/o Female	Fever Dyspnea Emesis Diarrhea Diffuse erythematous rash	Headache Blurry vision Abducens palsy	Bilateral papilledema	OP: >36 cm H_2O WBC:4 RBC:0 Glucose: 57 Protein: 37	CT: normal MRI: restricted diffusion of optic nerve sheaths, flattening of the posterior sclera, and eversion of the optic discs MR venography: flattening of the left transverse and sigmoid sinuses	IVIG IVMP Antibiotics Acetazolamide Hydrocortisone Aspirin LMWH	Discharged with clinical symptoms resolved Papilledema resolved 2 months later
	6 y/o Female	Fever Rash Conjunctivitis Cracked lips Emesis Diarrhea	Irritability Nuchal rigidity	-	OP:31 cm H_2O WBC:34 (34% neutrophils) RBC:0 Glucose: 98 Protein: 28	CT: cerebral edema	IVIG IVMP Antibiotics Aspirin LMWH Anakinra	Discharged with clinical symptoms resolved Papilledema resolved 5 months later
	13 y/o Female	Fever Abdominal pain Emesis	Encephalopathy Nuchal rigidity Headache	-	OP:>38 cm H_2O WBC:218 (90% neutrophils) RBC:6 Glucose: 58 Protein: 130	CT: normal MRI: normal	IVIG IVMP Hydrocortisone Antibiotics Aspirin LMWH Tocilizumab	Discharged with clinical symptoms resolved
	12 y/o Male	Fever Emesis Diarrhea	Encephalopathy Nuchal rigidity	-	OP:34 cm H_2O WBC:3 RBC:2 Glucose:137 Protein: 19	CT: normal	IVIG IVMP Antibiotics Aspirin LMWH	Discharged with clinical symptoms resolved
Current case	8 y/o Male	Fever Abdominal pain Vomiting Conjunctivitis	Headache Blurry vision	Bilateral papilledema	OP: 12 cm H_2O WBC: 0 RBC:0 Glucose: 55 Protein: 31	MRI: Flattening of the postrior sclera, distention of the perioptic nerve subarachnoid cerebrospinal fluid space, vertical tortuosity of the optic nerve. MR venography: normal	IVIG Antibiotics Acetazolamide Aspirin LMWH	Discharged with clinical symptoms resolved 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; RBC, red blood cell; WBC, white blood cell.

(CRP): 12 mg/L, procalcitonin: 0.19 μg/L, fibrinogen: 237 mg/dL, D-dimer: 4313 μg/L FEU, erythrocyte sedimentation rate: 26 mm/h, albumin: 2,7 mg/L, Pro-BNP: 1087 ng/L and troponin: 13 ng/L. A SARS-CoV-2 polymerase chain reaction (PCR) test from the nasopharyngeal swab was negative. SARS-CoV-2 serology was positive for IgM and IgG antibodies. His contrast-enhanced brain magnetic resonance imaging (MRI) showed signs of intracranial hypertension characterized by flattening of the posterior sclera, enlargement of the perioptic nerve subarachnoid cerebrospinal fluid space, vertical tortuosity of the optic nerve (Fig. 1) and MR venography was normal. Lumbar puncture (LP) demonstrated a normal opening pressure (12 cm H_2O) without pleocytosis and normal cerebrospinal fluid (CSF) glucose and protein levels, which indicated probable PTC. No viral or bacterial pathogens were detected in CSF PCR testing. According to the MIS-C definition provided by the CDC/WHO (1,5), our patient was considered MIS-C. The patient was treated with intravenous immunoglobulin (IVIG) 2 gr/kg for MIS-C and acetazolamide. Low molecular weight heparin treatment was initiated due to elevated D-dimer levels. Corticosteroids were not initiated because the patient did not show signs of shock, and his fever resolved after IVIG. On the second day of treatment, his headache and visual functions improved remarkably. On day 45, papilledema was completely regressed, and acetazolamide treatment was gradually tapered off.

DISCUSSION

We present an MIS-C case with symptoms of increased intracranial pressure. Several studies reported that most MIS-C patients present with gastrointestinal, cardiovascular and mucocutaneous symptoms.[7–9,11–13] Neurologic symptoms in MIS-C are rare manifestations when compared with other organ system involvements. Dufort et al[9] reported headache, altered mental status and confusion as neurologic symptoms were present in 13% of the patients 0–5 years of age and 38% of patients 13–20 years of age. Feldstein et al[11] also demonstrated that 21% of 186 MIS-C cases had neurologic symptoms.

The etiology of neurologic symptoms in SARS-CoV-2 infection and MIS-C have not been well described. Laboratory studies have shown that angiotensin-converting enzyme 2 (ACE2) is expressed in the brain.[14,15] Therefore, it is a potential target for the virus. Besides, the virus causes coagulation disorder, which increases the risk of thrombosis.[16] Schupper et al[17] presented two cases of MIS-C with neurologic manifestations due to a stroke caused by thrombosis. Therefore, we performed an MRI and MR venography to rule out a stroke and other neurologic disorders caused by thrombosis. Abdel-Mannan et al[18] presented four cases of severe MIS-C with encephalopathy. Their MRI findings were consistent with lesions in the splenium of the corpus callosum, which may also be observed in ischemia. Our patient had a headache and papilledema and elevated D-dimer levels at the presentation. His MRI showed signs of intracranial hypertension without thrombosis.

Papilledema is the swelling of optic nerves due to increased intracranial pressure, and if untreated, it may cause optic nerve damage and lead to loss of vision.[19] It is usually the hallmark of pseudotumor cerebri syndrome. Diagnostic criteria for definite pseudotumor cerebri syndrome are papilledema, regular neurologic examination except for abducens palsy, normal MRI findings and elevated opening pressure in LP. In some cases, like our case, LP opening pressure can be within expected ranges. In these cases, the diagnosis is considered probable pseudotumor cerebri.[20] Inflammatory disorders such as systemic lupus erythematosus and Kawasaki disease may present with increased intracranial pressure.[21–23] Becker et al[4] 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[23] 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 to previous cases, our patient was well and hemodynamically stable.[4,18,22] 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.

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