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Intracranial Hypertension in Multisystem Inflammatory Syndrome in Children

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Multisystem inflammatory syndrome in children (MIS-C) is characterized by fever and multiorgan system dysfunction. Neurologic complications of MIS-C are not well described. We present 4 patients with MIS-C who had intracranial hypertension and discuss the unique management considerations when this occurs concurrently with significant myocardial dysfunction. (J Pediatr 2021;233:263-7).

Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel pediatric disease that is being increasingly recognized by the medical community.1 Although coronavirus disease 2019 more commonly occurs in adults, MIS-C seems to be a clinical entity that predominates in children.2 The pathogenesis is not yet well-understood, but current evidence suggests MIS-C is caused by a rare but severe deleterious postinfectious inflammatory immune response after exposure to SARS-CoV-2. Common presenting symptoms include fever and gastrointestinal symptoms, followed in many cases by multiorgan system dysfunction and shock. Early in the pandemic, parallels were drawn between MIS-C and Kawasaki disease and Kawasaki disease shock syndrome owing to an overlap in symptomatology; however, over time, it has become clear that MIS-C is a distinct clinical entity.

Although the burden of gastrointestinal and cardiac manifestations in MIS-C has been described, few studies have characterized the spectrum and severity of acute neurologic dysfunction in this syndrome.1 Initial reports described neurologic dysfunction in up to two-thirds of children with MIS-C, including altered mental status, headache, and less commonly status epilepticus, stroke, and cerebral edema.3-11 Intracranial hypertension, with or without cerebral edema, has not been well-described as a complication of this syndrome.

Herein, we present 4 patients hospitalized at our institution between April 2020 and October 2020 with MIS-C complicated by intracranial hypertension and myocardial dysfunction (Table I) to inform clinicians of the occurrence of intracranial hypertension in patients with MIS-C and highlight unique hemodynamic management considerations in children with concurrent intracranial hypertension and myocardial dysfunction.

Case 1

A 14-year-old girl with a history of oppositional defiant disorder presented in April 2020 with dyspnea in the setting of 4 days of fever, headache, emesis, and diarrhea. Examination was significant for tachycardia and hypotension. She was ill-appearing and in moderate distress, with a diffuse erythematous rash and increased work of breathing. Initial laboratory results were notable for lactic acidosis, leukocytosis with lymphopenia and a bandemia, elevated inflammatory markers, hyponatremia, and acute kidney injury (Table II). A chest radiograph revealed diffuse multifocal opacities. A SARS-CoV-2 polymerase chain reaction (PCR) test was negative. SARS-CoV-2 serology was positive for immunoglobulin G (IgG) antibodies, although these results did not return until after discharge.

She received cefepime and doxycycline for possible toxic shock syndrome or tick-borne illness. The clinical course was complicated by respiratory failure and left ventricular dysfunction, for which she was intubated. She required epinephrine, norepinephrine, and hydrocortisone to obtain a goal mean
arterial pressure (MAP) of >65 mm Hg. Vasopressors were weaned off by hospital day (HD) 6 with normalization of myocardial dysfunction. On HD7, an echocardiogram revealed right coronary artery dilation, prompting treatment for presumed Kawasaki disease shock syndrome with aspirin, intravenous immunoglobulin (IVIG) 2 mg/kg, and a transition from hydrocortisone to intravenous methylprednisolone (IVMP) 2 mg/kg/day for 3 days followed by a taper.

On HD9, the patient noted blurry vision and was found to have a cranial nerve VI palsy and bilateral papilledema on ophthalmologic examination. Brain magnetic resonance imaging with and without contrast demonstrated restricted diffusion of optic nerve sheaths, flattening of the posterior sclera, and eversion of the optic discs, consistent with papilledema. Magnetic resonance venography demonstrated flattening of the left transverse and sigmoid sinuses, which

Table I. Selected patient data and treatment

| Cases (age, sex) | Neurologic signs or symptoms | LP | Brain imaging and/or EEG | Echocardiogram | Vasoactive infusions | Cytokine profile | Treatment |
|-----------------|-------------------------------|----|--------------------------|----------------|---------------------|-----------------|-----------|
| 1 (14 y/o F)    | Headache                      | OP: >36* | HCT: normal             | LV: moderate dysfunction | Epinephrine + + + soluble IL-2 | IVG            |          |
|                 | Blurry vision                 | WBC: 4 | MRV/AV: papilledema, flattened sinuses; otherwise normal | RV: no dysfunction | Norepinephrine             | IV              |          |
|                 | Cranial nerve                 | RBC: 0 |                         | RV: Coronary arteries: RCA dilation (z = 3.15) | Vasopressin        | IVMP§  |          |
|                 | Parietal palsy                | Protein: 37 |                         |                  | IL-10⁺⁺⁺ IFN-γ, IL-10⁺⁺⁺ | IL-6, TNF-α | Anakinra |
|                 | Papilledema                   | Oligoclonal bands: present |                         |                  |                      | IVMPI |  |
| 2 (6 y/o F)     | Irritability                  | OP: 31⁺ | HCT: cerebral edema; otherwise normal | LV: moderate dysfunction, mild dilation | Epinephrine + + + IFN-γ, IL-10⁺⁺⁺ | IVG x2 |          |
|                 | Nuchal rigidity               | WBC: 34 (34% neutrophils) | HCT (24 hours later): improved | RV: no dysfunction | Norepinephrine + IL-6, IL-8, TNF-α | IVMPI |  |
|                 |                               | RBC: 0 | EEG: no seizures         | Coronary arteries: no dilation | Milrinone             |                 |          |
|                 |                               | Glucose: 98 |                         |                  |                       |                 |          |
|                 |                               | Protein: 28 |                         |                  |                       |                 |          |
|                 |                               | SARS-COV-2 PCR: negative |                         |                  |                       |                 |          |
| 3 (13 y/o F)    | Encephalopathy                | OP: >38 | HCT: normal             | LV: moderate dysfunction, mild dilation | Epinephrine + + + IFN-γ, IL-6, IL-10⁺⁺⁺ | IVG |          |
|                 | Nuchal rigidity               | WBC: 218 (90% neutrophils) | MRV/AV: normal | RV: mild dysfunction | Norepinephrine + IL-6, IL-10⁺⁺⁺ | IVMP |  |
|                 |                               | RBC: 6 | EEG: no seizures         | Coronary arteries: no dilation | Vasopressin + TNF-α |                 |          |
|                 |                               | Glucose: 58 |                         |                  | Milrinone             |                 |          |
| 4 (12 y/o M)    | Encephalopathy                | OP: 34 | HCT: normal             | LV: moderate dysfunction, mild dilation | Epinephrine + + + IFN-γ, IL-6, IL-10⁺⁺⁺ | IVG |          |
|                 | Nuchal rigidity               | WBC: 137 | LV: mild dysfunction | RV: no dysfunction | Norepinephrine + IL-6, IL-8, TNF-α | IVMPII |  |
|                 |                               | RBC: 19 | EEG: no seizures         | Coronary arteries: no dilation | Milrinone             |                  |          |

On HD9, the patient noted blurry vision and was found to have a cranial nerve VI palsy and bilateral papilledema on ophthalmologic examination. Brain magnetic resonance imaging with and without contrast demonstrated restricted diffusion of optic nerve sheaths, flattening of the posterior sclera, and eversion of the optic discs, consistent with papilledema. Magnetic resonance venography demonstrated flattening of the left transverse and sigmoid sinuses, which

Table II. Selected initial laboratory data

| Laboratory values (unit) | Case 1 | Case 2 | Case 3 | Case 4 |
|--------------------------|--------|--------|--------|--------|
| Venous lactate (mmol/L)  | 6.4    | 2.1    | 2.6    | 2.5    |
| WBC count (10³/µL)       | 16.7   | 9.1    | 13.3   | 10.3   |
| Neutrophils (%)          | 21%    | 5%     | 13%    | 0%     |
| Procalcitonin (ng/mL)    | 15.3   | 70.0   | 1.5    | 38.1   |
| Serum sodium (mmol/L)    | 125    | 129    | 139    | 123    |
| Blood urea nitrogen (mg/dL) | 50    | 11    | 9     | 38     |
| Creatinine (mg/dL)       | 2.5    | 0.5    | 0.4    | 1.4    |
| Troponin (ng/mL)         | Not obtained | 0.30 | 0.01   | 4.4    |
| Brain natriuretic peptide (pg/mL) | Not obtained | 606.3 | 59.9  | 230.2  |

Values are initial value (reference range).
may also be seen with elevated intracranial pressure. A subsequent lumbar puncture (LP) revealed elevated opening pressure (>36 cm H2O; high normal pediatric range, 28 cm H2O) without pleocytosis (white blood cell [WBC] count). She was initiated on acetazolamide with subsequent improvement of her cranial nerve palsy.

The patient was discharged on HD15 to a rehabilitation facility on acetazolamide, aspirin, and a steroid taper. At the 2-month follow-up, papilledema and coronary artery dilation had resolved, acetazolamide and aspirin were discontinued, and she was at her neurologic baseline, without clinically evident deficits.

Case 2

A 6-year-old previously healthy girl presented in May 2020 with 4 days of fever as well as rash, conjunctivitis, cracked lips, emesis, and diarrhea (Table I). Examination was significant for altered mental status (irritability), tachycardia, hypotension, nuchal rigidity, scattered erythema, and a maculopapular rash. Initial laboratory results were notable for metabolic acidosis, anemia, lymphopenia, thrombocytopenia, elevated inflammatory markers, hyponatremia, hypokalemia, as well as elevated troponin and brain natriuretic peptide (Table II). The initial SARS-CoV-2 PCR test was negative, but repeat test on HD2 was positive (cycle threshold 40.2, suggesting a low viral load) and SARS-CoV-2 serology was positive for IgG antibodies. She was intubated in the setting of progressive shock and worsening encephalopathy. Hypertonic saline was administered as necessary to maintain serum sodium >140 mmol/L. Subsequent HCTs on HD2, HD3, and HD5 and brain magnetic resonance imaging with and without contrast on HD6 were normal. EEG demonstrated sedated sleep, without epileptiform abnormalities or seizures.

Her clinical course was complicated by rapidly progressive biventricular dysfunction with worsening lactatemia, requiring initiation of epinephrine, norepinephrine, vasopressin, milrinone, and stress-dosed hydrocortisone to maintain an initial goal MAP >85 mm Hg. This MAP goal was set to optimize cerebral perfusion pressure given her known intracranial hypertension and significant altered mental status, with neurologic examination being the primary clinical endpoint informing titration of therapies, an approach informed by our prior institutional experience of observing intracranial hypertension in our MIS-C population. Her mental status slowly returned to baseline, and sodium and MAP goals were liberalized by HD3. Vasopressors were weaned off by HD8, and echocardiogram showed normalization of her myocardial dysfunction.

The patient was treated with IVIG 2 mg/kg and IVMP 30 mg twice daily. In the setting of continued fever, systemic inflammation, and myocardial dysfunction, IVMP was increased to 1g daily for 3 days on HD4 followed by a taper. A serum cytokine panel showed an IL-6 level of >1300 pg/mL (high normal, 3. pg/mL), prompting administration of tocilizumab, an IL-6 inhibitor. She was initiated on enoxaparin and transitioned to aspirin. She was transferred to a rehabilitation facility on HD17 on a steroid taper and aspirin, and she was discharged home on HD27 at her neurologic baseline without clinically evident deficits.

Case 3

A 13-year-old previously healthy girl presented in August 2020 with 5 days of fever, headache, neck pain, myalgia, abdominal pain, and emesis (Table I). Examination was significant for fever, tachycardia, and hypotension and she was ill-appearing with waxing and waning mental status, neck tenderness, nuchal rigidity, and a diffusely tender abdomen. Her initial laboratory results were notable for lactic acidosis, leukocytosis with bandemia, anemia, thrombocytopenia, elevated inflammatory markers, and a coagulopathy (Table II). Abdominal ultrasound examination revealed hepatosplenomegaly, enlarged mesenteric lymph nodes, and moderate free pelvic fluid. SARS-CoV-2 PCR was negative and SARS-CoV-2 serology was positive for IgG antibodies. An LP obtained on HD1 showed elevated opening pressure (>38 cm H2O), pleocytosis (WBC count 218/µL with 90% segmented neutrophils), and elevated protein (140 mg/dL). She was initiated on broad-spectrum antibiotics, which were later narrowed to cefazidime and doxycycline for possible meningitis. She was intubated in the setting of progressive shock and worsening encephalopathy. Hypertonic saline was administered as necessary to maintain serum sodium >140 mmol/L. Subsequent HCTs on HD2, HD3, and HD5 and brain magnetic resonance imaging with and without contrast on HD6 were normal. EEG demonstrated sedated sleep, without epileptiform abnormalities or seizures.

Her clinical course was complicated by rapidly progressive biventricular dysfunction with worsening lactatemia, requiring initiation of epinephrine, norepinephrine, vasopressin, milrinone, and stress-dosed hydrocortisone to maintain an initial goal MAP >85 mm Hg. This MAP goal was set to optimize cerebral perfusion pressure given her known intracranial hypertension and significant altered mental status, with neurologic examination being the primary clinical endpoint informing titration of therapies, an approach informed by our prior institutional experience of observing intracranial hypertension in our MIS-C population. Her mental status slowly returned to baseline, and sodium and MAP goals were liberalized by HD3. Vasopressors were weaned off by HD8, and echocardiogram showed normalization of her myocardial dysfunction.

The patient was treated with IVIG 2 mg/kg and IVMP 30 mg twice daily. In the setting of continued fever, systemic inflammation, and myocardial dysfunction, IVMP was increased to 1g daily for 3 days on HD4 followed by a taper. A serum cytokine panel showed an IL-6 level of >1300 pg/mL (high normal, 3. pg/mL), prompting administration of tocilizumab, an IL-6 inhibitor. She was initiated on enoxaparin and transitioned to aspirin. She was transferred to a rehabilitation facility on HD17 on a steroid taper and aspirin, and she was discharged home on HD27 at her neurologic baseline without clinically evident deficits.

Case 4

A 12-year-old previously healthy boy presented in October 2020 with 2 days of fever and emesis in the setting of 5 days of diarrhea (Table I). Examination was significant for fever, tachycardia, and hypotension with waxing and waning mental status, conjunctivitis, cracked lips, nuchal
logic baseline, without clinically evident deficits. Initial laboratory results were notable for lactatemia, neutrophilic lymphopenic leukocytosis, elevated inflammatory markers, coagulopathy, hyponatremia, and acute kidney injury, as well as elevated troponin and brain natriuretic peptide (Table II). SARS-CoV-2 PCR was negative and SARS-CoV-2 serology was positive for IgG antibodies. HCT on HD1 was normal and an LP performed on HD2 showed an elevated opening pressure (34 cm H2O) without pleocytosis (WBC count of 3/µL). An EEG demonstrated diffuse slowing with poor organization, reactivity, and variability, but without epileptiform discharges or seizures. His clinical course was significant for biventricular dysfunction, for which he was intubated to decrease metabolic demand and initiated on milrinone and epi nphrine to maintain a goal MAP of >60 mm Hg.

The patient was treated with IVIG 2 mg/kg and IVMP 30 mg twice daily. IVMP was increased to 1g daily for 3 days on HD3 followed by a taper in the setting of continued myocardial dysfunction. He was initiated on enoxaparin and transitioned to aspirin. Vasopressors were weaned off on HD7 and subsequent echocardiogram showed normalization of myocardial dysfunction. He was discharged home on HD16 at his neurologic baseline, without clinically evident deficits.

Discussion

We present 4 patients admitted to our pediatric intensive care unit with MIS-C who demonstrated clinical, LP, and/or neuroimaging evidence of intracranial hypertension. Notably, each patient had ≥2 symptoms of neurologic dysfunction at presentation, including blurry vision, headache, neck stiffness, and encephalopathy. Similar to the existing MIS-C literature, each patient also had at least moderate myocardial dysfunction and required multiple vasopressors. All patients received immunomodulatory treatment with at least high-dose steroids and IVIG, and some received additional therapies. Although each had neuroimaging, none had dedicated cerebrovascular imaging to specifically look for the small vessel vasculitis seen in other MIS-C-related organ dysfunction. However, neuroimaging obtained did not reveal an alternate primary cause of their intracranial hypertension, including sinus venous thrombosis. All patients returned to their neurologic baseline, although one required acetazolamide for symptoms of intracranial hypertension at discharge.

These 4 patients were a subset of 30 total patients seen at our institution from April to November 2020 with a diagnosis of MIS-C. During this time period, 23 patients (77%) had neurologic symptoms with MIS-C, although isolated headache was the neurologic symptom in 17 of these patients. Other documented neurologic symptoms included encephalopathy or significant irritability, nuchal rigidity, numbn ess, and vision impairment. These were the only 4 patients with LPs obtained, as they were the only patients with papilledema (patient 1) or clinical concern for significant irritability or meningismus (patients 2-4; present on presentation).

The incidence of neurologic symptoms in MIS-C is not well-described in the literature, but it may be as high as 58% in small cohort studies and up to 71% in severe cases.6,7 Additionally, subtle neurologic symptoms may be missed in a critically ill child if they are unable to offer subjective complaints. Although the neurologic symptoms seen in MIS-C are similar to those seen in Kawasaki disease, the incidence seems to be higher in MIS-C, although further studies are needed to evaluate this observation.8 The etiology of these neurologic symptoms remains unclear, but is likely multifactorial. Among those LPs reported in patients with MIS-C, at least one-quarter were abnormal.3,4,16 However, these data are limited, because LPs may not be performed in affected patients with hemodynamic instability and, when they are, opening pressures are not always routinely obtained. Additionally, immunomodulatory treatment administered before LP may induce an aseptic meningitis subsequently incorrectly attributed to MIS-C.17 We do not believe that the medical management for MIS-C confounded our findings of intracranial hypertension in these patients because all but one demonstrated symptoms before the initiation of immunomodulatory therapies and one-half of the LPs were obtained before the start of these therapies. Regarding neuroimaging evaluation, one previous report described nonspecific T2 abnormalities in the spleen of the corpus callosum in 4 children with neurologic dysfunction in a larger cohort of 27 children with MIS-C.16 This case series suggests that intracranial hypertension may be one etiology of neurologic dysfunction that could go unrecognized; a high index of suspicion must therefore be maintained, even when presenting neurologic symptoms are nonspecific.

There is a high prevalence of myocardial dysfunction in patients admitted to the intensive care unit with MIS-C, with roughly one-half to three-quarters of patients requiring some form of inotropic support. The optimal management of this dysfunction requires that cardiac strain be minimized via afterload reduction while still meeting the minimum required driving pressure for adequate end-organ perfusion. Cerebral perfusion pressure is a function of MAP and intracranial pressure (cerebral perfusion pressure = MAP – intracranial pressure), such that if the intracranial pressure is higher than expected, there is a risk of underestimation of the MAP necessary to generate adequate cerebral perfusion pressure to prevent ischemic injury. Given our experience with this series of patients, we advocate for discussion of optimal MAP goals for patients with MIS-C with evidence of neurologic dysfunction and possible intracranial hypertension. Although optimal MAP targets are unknown, close monitoring of mental status, cerebral perfusion, and other clinical and laboratory markers of end-organ perfusion could aid in the assessment of perfusion pressure adequacy. Additionally, further consideration of higher serum sodium targets, acetazolamide, or other strategies used in other causes of intracranial hypertension should play in the management of these patients is warranted.
We present this case series of patients with MIS-C-associated intracranial hypertension to facilitate awareness of a critical complication of this disease that may impact systemic management and to raise questions requiring further investigation and discussion in the medical community. With a heightened clinical suspicion for intracranial hypertension and other neurologic manifestations of MIS-C, we hope to set the stage for a better understanding both of their incidence and of their impact on long term patient outcomes.

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