Case Report

Pseudotumor Cerebri Complicating Multisystem Inflammatory Syndrome in a Child

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Abstract

Purpose: To report a case of pseudotumor cerebri (PTC) in a child associated with multisystem inflammatory syndrome in children (MIS-C), associated with presumed coronavirus disease 2019.

Methods: A previously healthy 11-year-old female child presented with a 4-day history of fever, headache, vomiting, and loose stools. Laboratory investigations revealed neutrophilic leukocytosis, and markers of inflammation (C-reactive protein, ferritin, and interleukin-6) were significantly elevated. Pharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction was negative while anti-SARS-CoV-2 antibody was highly reactive. Ophthalmic evaluation for transient visual obscurations during hospital course revealed swelling of the optic disc in both eyes. Spectral-domain optical coherence tomography and ultrasonography confirmed the ophthalmoscopic findings. There was no neurologic deficit. Magnetic resonance imaging of the brain and magnetic resonance venogram revealed no structural lesion. The opening pressure of cerebrospinal fluid (CSF) was 336 mm of water, and CSF composition was normal.

Results: A diagnosis of PTC associated with MIS-C was made, and the child was treated with oral acetazolamide. Edema of the optic disc regressed following therapy, and the child is under follow-up.

Conclusions: PTC can occur in association with MIS-C. Clinicians need to be aware of this potential neuro-ophthalmic complication in MIS-C. Prompt diagnosis and treatment can prevent visual loss.

Keywords: COVID-19, Multisystem inflammatory syndrome in children, Pseudotumor cerebri

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Introduction

Pseudotumor cerebri syndrome (PTCS) is a disorder characterized by increased intracranial pressure of unclear etiology that carries significant morbidity and limited therapeutic options. PTCS can be primary otherwise called idiopathic intracranial hypertension (IIH) or secondary, attributable to a number of medical conditions and drugs. This neurologic syndrome predominantly affects obese women of reproductive age group, and clinical features include symptoms and signs of raised intracranial pressure with normal cerebrospinal fluid (CSF) composition and no structural abnormality on brain imaging.[1] PTCS is relatively uncommon in children and is associated with variable risk factors and clinical presentation.[2] We report a case of PTCS in a child associated with multisystem inflammatory syndrome in children (MIS-C), temporally associated with coronavirus disease 2019 (COVID-19).

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Case Report

An 11-year-old girl with no significant past medical history was brought to the emergency department with complaints of fever over the past 4 days associated with headache, vomiting,

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abdominal pain, and loose stools. There was associated lethargy but no history of seizures, altered sensorium, or respiratory symptoms. There were no sick contacts. At admission, the child had a temperature of 39°C, heart rate of 112 beats/min, and oxygen saturation of 100% on room air. Body mass index was 16 kg/m^2. Physical examination was unremarkable except for bilateral conjunctival congestion. Investigations revealed decreased hemoglobin, leukocytosis with neutrophilia, and elevated inflammatory markers including ferritin, interleukin-6 (IL-6), and C-reactive protein. Blood and urine cultures were negative, and liver function tests were found to be normal. Nasopharyngeal and oropharyngeal swabs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time polymerase chain reaction (RT-PCR) were negative. Serologic testing for SARS-CoV-2 antibodies by chemiluminescence immunoassay was highly reactive (observed titer – 212, ≥1 being labeled reactive) suggestive of SARS-CoV-2 infection. Table 1 shows the laboratory parameters. Echocardiogram was normal. On day 3 of admission, the child complained of transient obscurations of vision lasting for a few seconds associated with change in posture, and was referred for ophthalmic consultation.

On examination, uncorrected visual acuity was 20/20, and color vision was normal in both eyes. Anterior segment examination was unremarkable, and pupillary responses were normal. Extraocular movements were full. Fundus examination revealed optic disc swelling in both eyes [Figure 1a]. Neurologic examination was otherwise normal. Visual field evaluation by automated perimetry (Humphrey field analyzer) was found to be unreliable due to extensive fixation losses. Spectral-domain optical coherence tomography (OCT) showed increased thickness of peripapillary retinal nerve fiber layer (RNFL) in both eyes in all the four quadrants confirming edema of the optic disc [Figure 2a]. Magnetic resonance imaging of the brain and magnetic resonance venography (MRV) revealed normal ventricles, brain parenchyma, and venous sinuses. Transorbital ultrasound revealed bulging optic disc in both eyes. The optic nerve sheath diameter (ONSD) measurements obtained 3 mm posterior to the globe were found to be 5.6 mm in the right eye and 6 mm in the left eye [Figure 3a]. Lumbar puncture revealed a CSF opening pressure of 336 mm of water. CSF cultures were negative, and biochemistry was normal.

Since the child was hemodynamically stable and not hypoxic (SpO_2 100% on room air) at admission as well as during hospital course, she was managed with empiric broad-spectrum antibiotic therapy (intravenous ceftriaxone 2 g for 7 days) along with supportive care for fever (paracetamol) and loose stools (intravenous fluid replacement). As serial IL-6 and serum ferritin showed declining trend, the child was treated only with supportive measures. A diagnosis of pseudotumor cerebri (PTC) associated with MIS-C was made, and the child was started on oral acetazolamide 500 mg twice daily. By 4 weeks, headache and transient visual obscurations had subsided. Visual acuity remained 20/20, and fundus examination revealed resolving disc edema. The dose of oral acetazolamide was reduced to 250 mg thrice daily. At her last visit, 7 weeks since her initial presentation, she was found to have visual acuity of 20/20 and resolved disc edema in both eyes [Figure 1b]. Follow-up OCT revealed normalization of peripapillary RNFL thickness [Figure 2b]. The ONSD measurements were found to be 4 mm in both eyes at follow-up [Figure 3b]. The dose of acetazolamide has been tapered further, and she is under follow-up.

Table 1: Laboratory parameters of the patient and reference range

Parameter	Value	Reference range
Hemoglobin (g/dL)	10.5	11.5-15.5
White blood cell count (10^3/μL)	17	5-13
Neutrophil (%)	91.1	45-65
Lymphocyte (%)	7.5	32-52
Erythrocyte sedimentation rate (mm/h)	31	4-12
C-reactive protein (mg/dL)	39	<0.6
Serum ferritin (ng/mL)	352.4	7-140
IL-6 (pg/mL)	197.8	<7
NT-proBNP (pg/mL)	1163	<125
D-dimer (mg/L FEU)	1.48	<0.5
Anti-SARS-CoV-2 titer	212	<1

IL-6: Interleukin-6, NT-proBNP: N-terminal-pro-brain natriuretic peptide, Anti-SARS-CoV-2: Antibody against severe acute respiratory syndrome coronavirus 2

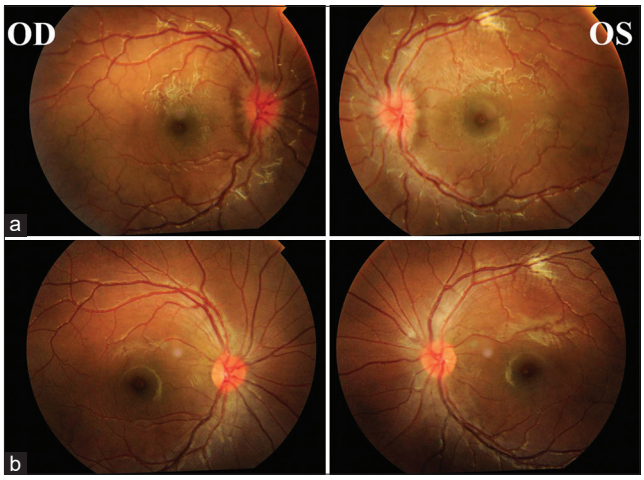

Figure 1: (a) Fundus photograph both eyes showing edema of optic disc. (b) Fundus photograph both eyes showing resolved disc edema at follow-up

Discussion

MIS-C, also called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, is a life-threatening condition that can lead to multi-organ dysfunction and long-term sequelae. The clinical features of MIS-C include severe illness necessitating hospitalization, fever, and involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection.[3] Our

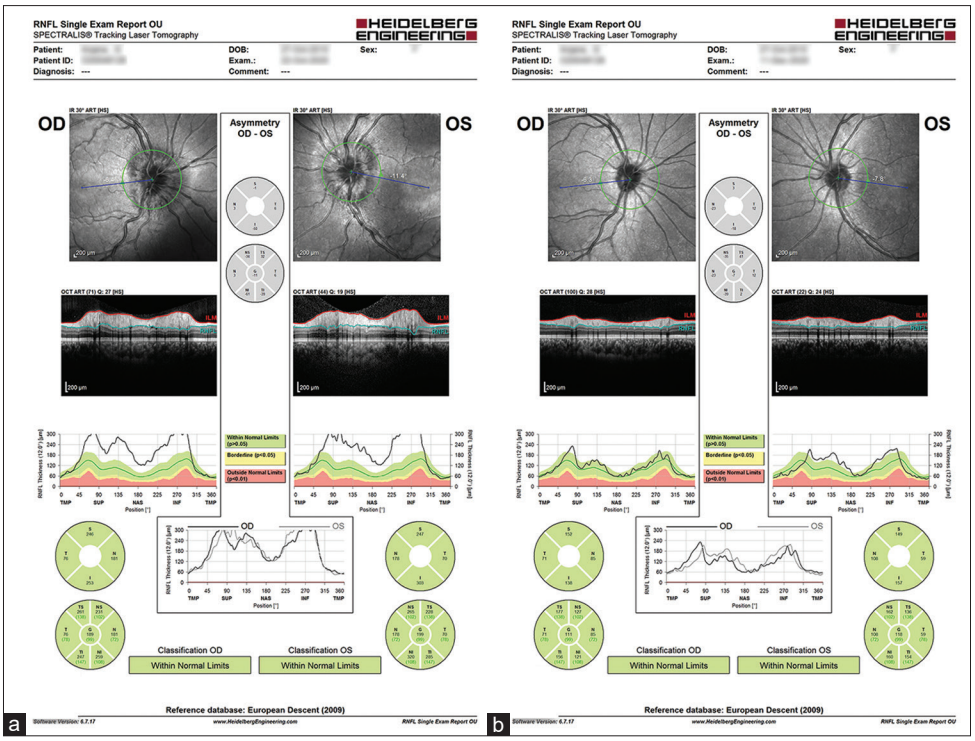

Figure 2: (a) Spectral-domain optical coherence tomography (SD-OCT) showing increased thickness of peripapillary retinal nerve fiber layer (RNFL) in both eyes. (b) SD-OCT both eyes at follow-up showing normalization of peripapillary RNFL thickness

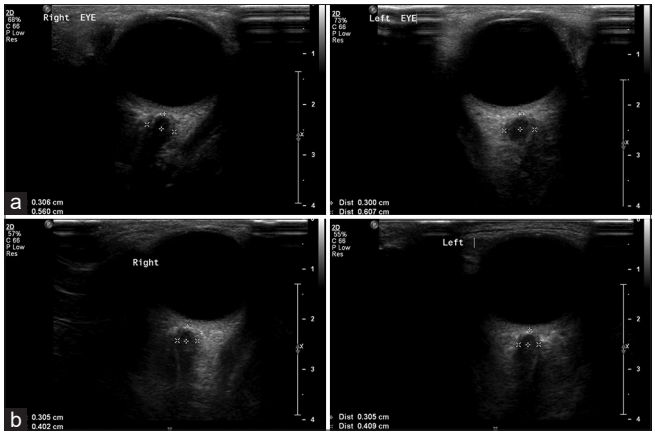

Figure 3: (a) Transorbital ultrasound showing increased optic nerve sheath diameter (ONSD) 3 mm posterior to inner scleral surface; 5.6 mm in the right eye and 6 mm in the left eye. (b) Transorbital ultrasound at follow-up showing normalization of ONSD; 4 mm in both eyes

patient was found to meet all the criteria specified in the Centers for Disease Control and Prevention and World Health Organization case definitions of MIS-C.[4,5]

The pathophysiology of MIS-C is unclear, and possible mechanisms include T-cell or antibody recognition of self-antigens resulting in autoantibodies, immune response against viral antigens expressed on infected cells and formation of immune complexes activating inflammation as well as viral superantigen sequences which activate host immune cells.[6] Dysregulated hyperinflammation is a critical event in the pathogenesis of MIS-C, and this condition is frequently associated with gastrointestinal symptoms and cardiovascular dysfunction.[7]

Although neurologic manifestations have been documented during acute phase of infection with SARS-CoV-2,[8,9] involvement of the central nervous system is uncommon in MIS-C. The neurologic features of MIS-C have been strongly suggested to represent a postinfectious immune response, and manifestations reported include headache, encephalopathy, and aseptic meningitis.[10]

We had not performed RT-PCR for SARS-CoV-2 on CSF since our patient showed evidence of previous infection with SARS-CoV-2 rather than current infection (pharyngeal swab was negative while antibodies to SARS-CoV-2 were present). Only one-third of cases of MIS-C have been reported to be positive by RT-PCR for SARS-CoV-2. The delayed presentation of MIS-C relative to the pandemic curve, a low proportion of cases who were SARS-CoV-2 positive by RT-PCR, and a high proportion who were antibody positive suggest that this inflammatory syndrome is not mediated by direct viral invasion but coincides with the development of acquired immune responses to SARS-CoV-2.[6] Previous studies have noted the absence of SARS-CoV-2 RNA in CSF analysis of COVID-19 patients with neurological symptoms suggesting that indirect mechanisms are responsible for neurologic manifestations in these patients.[11,12]

Although the symptoms of PTCS in children are similar to that of adults, the demographics vary, and children are reported to

have a higher incidence of secondary PTC. A distinct seasonal variation has been reported in the clinical presentation of IIH in prepubertal children, suggesting a possible association between IIH and concurrent infections in this age group.[13] Agraz *et al*. have noted a high incidence of atopy in their study cohort of children with PTC, suggesting that autoimmune component may play a role in pediatric population.[2]

To the best of our knowledge, four similar cases of PTCS associated with MIS-C (two case reports and a case series of two patients) have been reported in literature.[14-16] Although two patients had received therapy with doxycycline and steroids, the short course and recent initiation preclude the possibility of these medications contributing to increased intracranial pressure.

The mechanism behind the occurrence of PTCS in association with MIS-C is unclear. It has been postulated that increased intracranial pressure reflects systemic inflammation related to SARS-CoV-2 infection, resulting in central nervous system effects.[16] It is of interest to note that obesity, the most striking risk factor for PTCS, is associated with dysregulation of several inflammatory cytokines and aberrant glucocorticoid metabolism through manipulation of the enzyme 11-beta-hydroxysteroid dehydrogenase (11β-HSD).[17] 11β-HSD is a bidirectional enzyme that regulates prereceptor corticosteroid availability and glucocorticoid availability in the central nervous system that is one of the factors pivotal to intracranial pressure homeostasis. Among the two isoforms, 11β-HSD1 activates cortisol from cortisone while the isoform 11β-HSD2 inactivates cortisol. It is well established that several inflammatory cytokines such as tumor necrosis factor-α and ILs 1 and 6 are potent activators of 11β-HSD1.[18]

We speculate that PTC associated with MIS-C can be multifactorial, and one another possibility could be aberrant glucocorticoid metabolism as a result of cytokine storm and 11β-HSD1 activity. Increased 11β-HSD1 activity has been shown to influence the pathogenesis of PTC through manipulation of CSF dynamics at the level of choroidal plexus as well as arachnoidal granulations.[19] Further studies are warranted in this regard.

Few cases of isolated intracranial hypertension in association with active SARS-CoV-2 infection have been reported in adults. The proposed pathophysiologic mechanisms for intracranial hypertension include acute encephalitis, venous sinus thrombosis, intracranial venous congestion due to inflammation as a result of SARS-CoV-2 infection, and the associated coagulopathy as well as hyperviscosity state leading to impaired absorption of CSF.[20,21] The absence of clinical features such as altered sensorium/seizures and normal brain parenchyma evident on neuroimaging in our patient ruled out encephalitis. Normal MRV ruled out venous sinus thrombosis in our patient.

The other possible etiologies of swelling of optic disc in the setting of SARS-CoV-2 infection include optic neuritis, ischemic optic neuropathy, papillophlebitis, and retinal vein occlusion. The presence of normal visual acuity and color vision along with normal pupillary responses and the absence of associated retinal hemorrhages or venous tortuosity in our patient made us exclude these causes.

Prompt diagnosis and treatment of PTCS is essential since it can lead to irreversible visual loss. Although the pathophysiology remains unclear, clinicians should be aware of this potential complication with MIS-C. Fundus examination is valuable as part of a multidisciplinary approach toward management of MIS-C.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 2013;81:1159-65.
2. Agraz D, Morgan LA, Fouzdar Jain S, Suh DW. Clinical features of pediatric idiopathic intracranial hypertension. Clin Ophthalmol 2019;13:881-6.
3. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) following SARS-CoV-2 infection: Review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel) 2020;7:69.
4. Centers for Disease Control and Prevention. Emergency Preparedness and Response: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Health Advisory. Available from: https://emergency.cdc.gov/han/2020/han00432.asp. [Last accessed on 2020 Dec 26].
5. World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19: Scientific Brief; 2020. Available from: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. [Last accessed on 2020 Dec 26].
6. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, *et al.* COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20:e276-88.
7. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, *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. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90.
9. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, *et al.* Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;87:18-22.
10. Chen TH. Neurological involvement associated with COVID-19 infection in children. J Neurol Sci 2020;418:117096.
11. Bellon M, Schweblin C, Lambeng N, Cherpillod P, Vazquez J,

Lalive PH, *et al.* Cerebrospinal fluid features in SARS-CoV-2 RT-PCR positive patients. Clin Infect Dis 2020;ciaa1165.
12. Neumann B, Schmidbauer ML, Dimitriadis K, Otto S, Knier B, Niesen WD, *et al.* Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. J Neurol Sci 2020;418:117090.
13. Distelmaier F, Tibussek D, Schneider DT, Mayatepek E. Seasonal variation and atypical presentation of idiopathic intracranial hypertension in pre-pubertal children. Cephalalgia 2007;27:1261-4.
14. Verkuil LD, Liu GT, Brahma VL, Avery RA. Pseudotumor cerebri syndrome associated with MIS-C: A case report. Lancet 2020;396:532.
15. Parsons E, Timlin M, Starr C, Fries A, Wells R, Studer M, *et al.* MIS-C in February 2020 and implications of genomic sequencing for SARS-CoV-2. J Pediatric Infect Dis Soc 2020;10:695-97.
16. Baccarella A, Linder A, Spencer R, Jonokuchi AJ, King PB, Maldonado-Soto A, *et al.* Increased intracranial pressure in the setting of multisystem inflammatory syndrome in children, associated with COVID-19. Pediatr Neurol 2021;115:48-9.
17. Sinclair AJ, Ball AK, Burdon MA, Clarke CE, Stewart PM, Curnow SJ, *et al.* Exploring the pathogenesis of IIH: An inflammatory perspective. J Neuroimmunol 2008;201-202:212-20.
18. Chapman KE, Coutinho AE, Zhang Z, Kipari T, Savill JS, Seckl JR. Changing glucocorticoid action: 11β-hydroxysteroid dehydrogenase type 1 in acute and chronic inflammation. J Steroid Biochem Mol Biol 2013;137:82-92.
19. Sinclair AJ, Walker EA, Burdon MA, van Beek AP, Kema IP, Hughes BA, *et al.* Cerebrospinal fluid corticosteroid levels and cortisol metabolism in patients with idiopathic intracranial hypertension: A link between 11beta-HSD1 and intracranial pressure regulation? J Clin Endocrinol Metab 2010;95:5348-56.
20. Svedung Wettervik T, Kumlien E, Rostami E, Howells T, von Seth M, Velickaite V, *et al.* Intracranial pressure dynamics and cerebral vasomotor reactivity in coronavirus disease 2019 patient with acute encephalitis. Crit Care Explor 2020;2:e0197.
21. Silva MT, Lima MA, Torezani G, Soares CN, Dantas C, Brandão CO, *et al.* Isolated intracranial hypertension associated with COVID-19. Cephalalgia 2020;40:1452-8.