ACUTE CEREBELLITIS IN MIS-C

A Case Report

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Background: Coronavirus disease-2019 (COVID-19) is characterized predominantly by respiratory symptoms and has affected a small subset of children. Multisystem inflammatory syndrome in children (MIS-C) has been reported in children following COVID-19. There is increasing report that COVID-19 may also lead to neurologic manifestations. Cerebellar lesions may be observed in viral infections.

Case report: We report a child with MIS-C related to severe acute respiratory syndrome coronavirus 2, who developed cerebellar lesion during the disease course. Encephalopathy was the first central nervous system symptom. His consciousness improved but he developed clinical signs of cerebellar dysfunction including ataxia, dysarthria and nystagmus. Brain magnetic resonance imaging (MRI) revealed symmetrical pathological signal changes in both cerebellar hemispheres.

Conclusion: We demonstrated the first child with MIS-C to develop cerebellar lesion on brain MRI, suggestive of cerebellitis.

Key Words: Cerebellitis, child, COVID-19, MIS-C

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to substantial morbidity and mortality in adults. Although, COVID-19 is more likely to be asymptomatic or has a mild to moderate disease course in children, severe cases and multisystem inflammatory syndrome in children (MIS-C) were reported as well. Serious complications may occur in conjunction with both acute SARS CoV-2 infection and MIS-C.[1,2] However, there is increasing report that COVID-19 may also lead to neurologic manifestations. Headache, meningism/meningitis, encephalopathy/encephalitis, seizures, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, cerebellar ataxia, postinfectious brainstem encephalitis, myositis, global proximal muscle weakness, Guillain-Barre syndrome, bulbar palsy and anosmia have been defined as the neurologic manifestations of SARS-CoV-2 in children.[3–7] Herein, we aim to report a child with cerebellitis associated with SARS-CoV-2.

CASE REPORT

A 3-year-old previously healthy child presented with fever for 10 days. He had rash, nausea-vomiting, diarrhea and altered mental status for the last 2 days. He did not have COVID-19 contact history. He was admitted to pediatric intensive care unit with a provisional diagnosis of MIS-C. His body temperature was 38.6°C, heart rate was 157 beats/min, blood pressure was 73/43 mm Hg, respiratory rate was 44 breaths/min and oxygen saturation was 95% at room air, on admission. He was unconscious and disoriented, Glasgow Coma Scale was 11 (E 3, V 4 and M 4), both pupils were reactive to light. Meningeal irritation signs were positive. He had a diffuse retiform purpura localized over the lower extremities and chilblain-like acral lesion, bilateral conjunctivitis, papillitis of the tongue, lip cracking and fissuring. He was tachycardic with a 2/6 systolic murmur and lung auscultation revealed bilateral widespread crackles and decreased breath sounds. He was intubated because of respiratory failure and mechanical ventilation commenced. SARS CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab was negative. Laboratory findings showed elevated inflammatory markers along with positive SARS-CoV-2 antibody testing, fulfilling the criteria for MIS-C (Table 1). Brain magnetic resonance imaging (MRI) was normal (Fig. 1). Background electroencephalogram (EEG) activity was abnormal. Diagnostic lumbar puncture was performed successfully. Cerebrospinal fluid (CSF) analysis did not reveal pleocytosis, protein level was 44 mg/dl, and glucose level was 35 mg/dl when serum glucose level was 55 mg/dl. SARS-CoV-2 PCR was negative in CSF. Echocardiography (ECHO) showed ventricular systolic dysfunction and left ventricular ejection fraction was 30% with mitral insufficiency. Fluid replacement therapy, milrinone (0.5µg/kg/min), adrenaline and noradrenaline infusions were started because of hypotension. Antimicrobial therapy was initiated as cefotaxime, vancomycin and acyclovir. He received intravenous immunoglobulin (1 g/kg for 2 days) and high-dose corticosteroids (30 mg/kg for 5 day) followed by a prednisone taper. On day 5, the respiratory and hemodynamical parameters were stabilized and inotrope infusions were weaned off. CSF culture was sterile. Meningitis/encephalitis panel (*Cryptococcus neoformans*/*Cryptococcus gattii*, Cytomegalovirus, Enterovirus, *Escherichia coli* K1, *Haemophilus influenza*, Herpes simplex virus 1, Herpes simplex virus 2, Human herpesvirus 6, Varicella zoster virus, Human parechovirus, *Listeria monocytogenes*, *Neisseria meningitides*, *Streptococcus agalactiae* and *Streptococcus pneumonia*) was negative. On day 6, he was extubated and control ECHO was normal. His consciousness improved but he developed clinical signs of cerebellar dysfunction including ataxia, dysarthria and nystagmus. Brain MRI was repeated and revealed symmetrical pathological signal changes in both cerebeller hemispheres, suggesting diffusion restriction (Fig. 1). Prednisone continued as 2 mg/kg/day. The patient improved gradually and was discharged on day 16 with prednisone and aspirin (100 mg/day) treatments. He remained symptom-free and at his cognitive baseline at 1-month follow-up after discharge.

DISCUSSION

We, herein, report a previously healthy child who met the criteria for MIS-C and developed reversible encephalopathy with EEG disorganization and bilateral cerebellar lesions, which improved with intravenous immunoglobulin and steroid.

In a multinational, multicenter, collaborative study revealing neuroimaging manifestations in children with SARS-CoV-2 and encephalopathy; the most common findings were acute disseminated encephalomyelitis-like changes of the brain, myelitis and neural enhancement. Cerebrovascular complications in children were rare according to adults. Splenial lesions and myositis were predominantly observed in children with MIS-C.[8] Akcay et al[7] reported two children with acute disseminated encephalomyelitis-like disease presented with encephalopathy. Bektas et al[9] published a case series on two children who had MRI changes involving the splenium of the corpus callosum and who presented with fever, rash and shock. Reversible lesions of the corpus callosum have been

TABLE 1. Changes in Biochemical, Hematologic Findings and Treatment of the Patient

Variables	On admision	12th hour	24th hour	36th hour	48th hour	60th hour	72th hour	HD 4	HD 5	HD 6	HD 7	HD 8	HD 9	HD 11	HD 15
WBC count, $\times 10^3/\mu L$	11.90	8.23	11.50	13.80	16.40	15.93	13.02	7.38	5.23	8.35	10.82	11.22	10.85	12.68	14.50
Neutrophil, $\times 10^3/\mu L$	11.09	7.40	10.40	12.50	14.60	13.43	10.67	5.40	3.34	5.60	7.67	7.16	6.10	7.80	10.40
Lymphocyte, $\times 10^3/\mu L$	0.55	0.66	0.83	0.95	1.44	2.08	1.88	1.40	1.60	1.99	2.12	2.78	3.09	3.20	2.80
Hemoglobulin, g/dl	11.9	8.8	8.2	8.0	7.0	11.1	11.3	10.7	9.3	8.8	10.7	10.4	9.8	10.1	12.5
Platelets, $\times 10^3/\mu L$	72	46	31	19	13	12	6	8	56	41	57	98	184	305	365
Glucose, mg/dl	55	115	98	134	144	135	274	172	147	123	129	–	77	104	97
BUN, mg/dl	35	36	46	53	62	67	70	65	57	44	28	16	16	20	18
Creatinine, mg/dl	1.06	1.16	1.26	1.68	1.73	2.12	2.00	1.20	1.09	0.56	0.59	0.36	0.36	0.40	0.29
Total bilirubin, mg/dl	2.00	1.86	2.20	1.96	2.71	3.62	4.88	7.26	3.10	1.63	1.51	1.28	1.08	0.90	0.66
AST, U/L	384	250	191	156	172	178	183	187	169	89	61	41	29	33	28
ALT, U/L	175	120	95	86	88	95	109	107	109	93	80	61	54	43	22
Uric acid, mg/dl	8.3	9.2	9.3	8.7	–	6.3	5	3.4	3.6	3.7	2.4	1.6	1.7	1.9	1.9
CK, U/L	119	200	232	800	4144	5233	3505	1956	1464	491	–	–	–	192	165
ALP, U/L	208	153	–	152	163	–	262	417	356	244	225	–	194	193	185
LDH, U/L	633	531	539	526	618	675	657	653	697	627	671	593	536	488	–
Sodium, mmol/L	132	145	155	150	147	148	150	153	147	147	140	3135	134	133	133
Potassium, mmol/L	5.29	4.86	4.26	3.96	4.20	3.92	3.17	2.86	2.94	3.71	4.7	5.00	5.00	4.97	4.62
Total protein, g/dl	4.86	6.50	4.85	5.40	6.50	6.73	6.73	6.93	7.14	6.98	6.85	7.25	7.30	9.70	8.50
Albumin, g/dl	2.56	3.40	2.86	2.53	2.70	3.08	2.96	3.38	3.36	3.34	3.48	3.72	3.70	4.40	4.20
CRP, mg/L	100	84	102	110	119	113	99	64	45	24	13	7	4	3	9
Pro-calcitonin, ng/mL	1054	720	720	>100	>100	>100	102	48	14	3.24	1.59	1.00	0.78	0.51	0.27
PT, s	30.3	27.4	18.9	26.8	14.7	14.8	14.8	14.7	16.1	16.1	16.6	15.3	–	13.7	11.3
PT INR	2.47	2.22	1.50	2.17	1.15	1.14	1.15	1.14	1.26	1.30	1.3	1.19	–	1.06	0.86
aPTT, s	64	53	40	49	48	37	46	30	29	29	29	28	–	30	26
D-dimer, μg/mL (FEU)	14.0	12.9	13.1	13.8	11.4	15	9.0	15.3	8.3	4.8	3.4	3.4	–	1.6	1.6
Fibrinogene, mg/dl	292	275	243	235	246	248	209	178	183	147	165	212	–	353	489
Pro-bnp, ng/L	>35000	>35000	–	21385	15839	10160	10160	8143	6173	5929	6742	2898	–	459.3	163.8
Ferritin, μg/L	1001	–	519	475	467	–	636	687	–	–	740	657	–	–	857
Troponin, ng/L	10.38	12.44	–	87.34	–	166.8	85.43	133.2	77.6	68.5	59.6	46.3	–	45.35	20.23
VIS	15	25	65	55	90	45	42.5	17.5							
Adrenalin	–	–	0.10	–	0.10	–	–	–	–	–	–	–	–	–	–
Noradrenalin	0.10	0.20	0.50	0.50	0.75	0.40	0.40	0.15	–	–	–	–	–	–	–
Milrinon	0.50	0.50	0.50	0.50	0.50	0.50	0.25	0.25	0.25	–	–	–	–	–	–
Treatment	30 mg/kg MP 1 g/kg IVIG	–	30 mg/kg MP 1 g/kg IVIG		30 mg/kg MP		30 mg/kg MP	30 mg/kg MP	2 mg/kg MP	2 mg/kg MP	2 mg/kg MP	2 mg/kg MP	2 mg/kg MP	1 mg/kg MP	0.5 mg /kg MP

ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; CK, creatine kinase; CRP, C-reactive protein; FEU, fibrinogen equivalent units; HD, hospital day; INR, international normalized ratio; LDH, lactate dehydrogenase; MP, methylprednisolone; PT, prothrombin time; VIS, vasoactive-inotropic score; WBC, white blood cell.

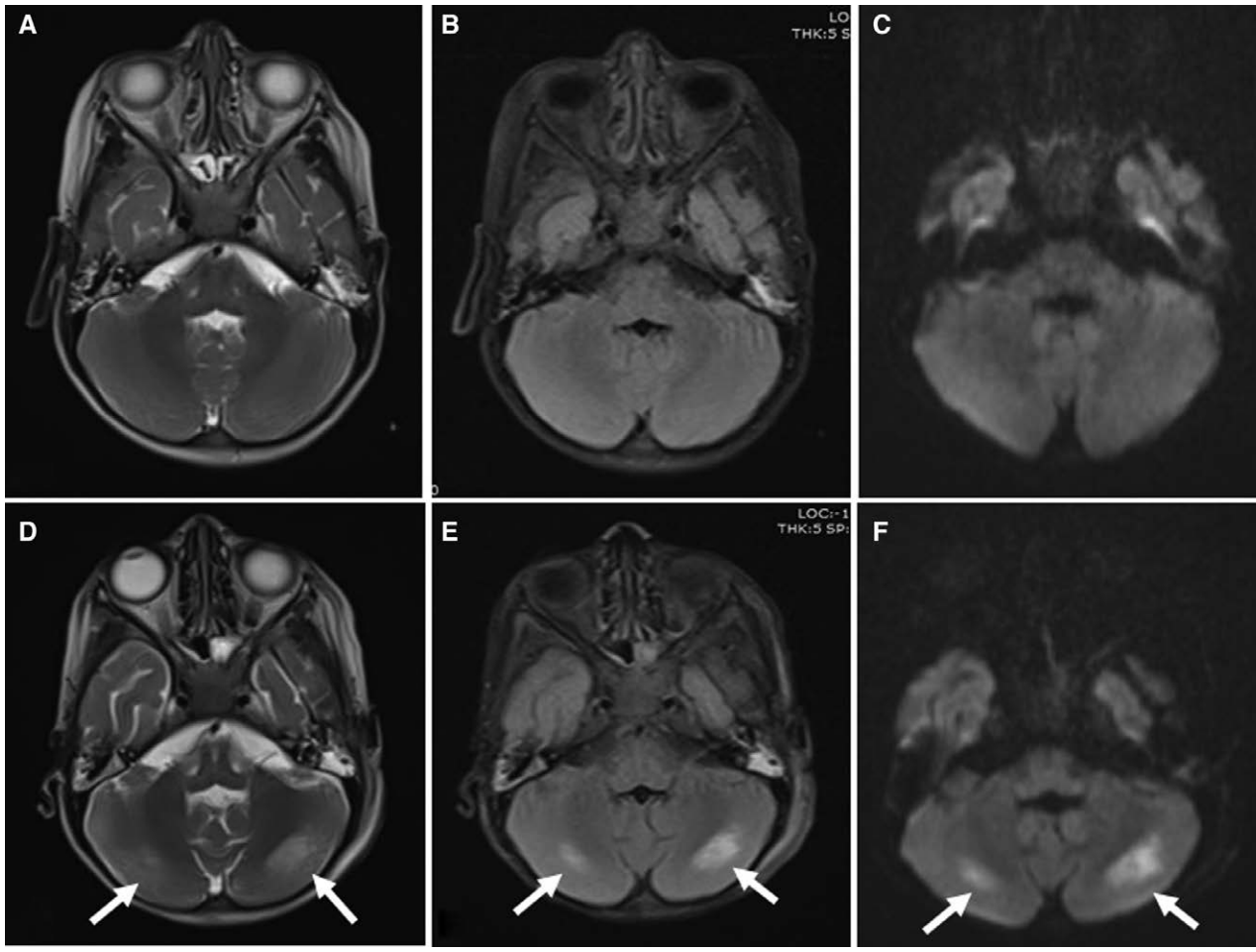

FIGURE 1. Brain MRI of patient. T2A (A), FLAIR (B) and DWI (C) sequences in the cranial MRI examination of the case taken during the first admission no pathology was observed. However, in the control cranial MRI taken 6 days later, symmetrical pathological signal changes were observed in T2W (D) and FLAIR (E) sequences in both cerebral hemispheres, and these lesions showed restriction in DWI (F). MRI indicates magnetic resonance imaging.

observed in MIS-C. Although COVID-19-associated cerebellitis has been observed in children, the association of MIS-C and cerebellitis has not been reported before. Sharma et al mentioned about two children with cerebellitis-associated acute COVID-19 infection.[10] The patient achieved a rapid clinical recovery therefore control MRI was not performed and this was a limitation to our case report.

In conclusion, given the prevalence of MIS-C, clinicians must investigate the underlying etiology of MIS-C-associated neurologic manifestations and the appropriate therapies for these patients.

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The written inform consent to publication has been obtained from the parents.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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