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RESEARCH ARTICLE

Severe Neurological Manifestations of Multisystem Inflammatory Syndrome in Adults (MIS-A)

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Disclosures- None

ABSTRACT

Introduction; Multi-system inflammatory syndrome (MIS) is a para infectious or post infectious extra-pulmonary complication of COVID-19. Neurological complications are better described in children with multi-system inflammatory syndrome (MIS) in children (MIS-C). There is a paucity of literature about severe neurological manifestations of multi-system inflammatory syndrome in adults (MIS-A).

Methods; Over a 22-month period, from June 2020 to December 2021, over 3450 COVID patients were admitted to our institution including 900 patients in the medical and COVID ICUs. Ten patients (1.1%) presented to us with MIS-A with severe neurological manifestations.

Results; Severe neurological manifestations included transverse myelitis, COVID encephalitis, acute encephalopathy, status epilepticus and rhabdomyolytic myopathy. Our cohort had a high morbidity and mortality rate.

Conclusions; Most patients with MIS-A had severe neurological involvement and a poor outcome.

Keywords: Multisystem inflammatory syndrome in adults; MIS-A, neurological; MIS-A, India; COVID reinfection, MIS-A

Introduction

Some patients with acute COVID-19 illness develop a hyperinflammatory storm (COVID-HIS) with severe lung injury and multi-organ dysfunction. A minority of admitted COVID-19 patients present with a severe primary extra-pulmonary multisystem inflammatory syndrome (MIS) (<1.7%).[1] In contrast to COVID-HIS, pulmonary manifestations, respiratory failure, or hypoxia are modest in MIS. MIS seems to be a para or post-infectious hyperinflammatory complication of COVID-19. Initially, this syndrome was described in children (MIS-C) with cardiogenic shock, prominent gastrointestinal and dermatological features, elevated inflammatory markers, resembling Kawasaki disease (KD) or Toxic shock syndrome (TSS).[2,3,4] In MIS-C, around 27% of patients develop neurological manifestations, including include headaches, meningitis, encephalopathy, seizures, ataxia or proximal muscle weakness. [5]

Initially described in children (MIS-C), MIS is now well recognized in adults (MIS-A). Case definitions of MIS-A are now established.[1,6] With prominent cardiac or multi-system involvement, MIS-A is usually managed in medical Intensive care units (ICU) and neurological findings are infrequently reported. Neurological features comprise headache, encephalopathy or large vessel occlusion (LVO), and stroke. However, it is now evident that the clinical spectrum of MIS-A is broader than originally envisaged.[Error! Bookmark not defined.] Patients may present with multi-organ dysfunction without severe cardiovascular involvement.[7]

Methods

Over a 22-month period, [June 2020 to December 2021], over 3450 COVID patients were admitted to our institution including 900 patients in the medical and COVID ICUs. Ten patients with MIS-A with severe neurological manifestations were diagnosed during this period and were identified from case records of primary admissions to the neurology ICU as well as through neurology consultations from the COVID-19 ICU. Severe manifestations were defined as acute encephalopathy, encephalitis, stroke, meningitis, Guillain-Barre syndrome, seizures, ICU acquired weakness or unexplained neurological symptoms. This was a retrospective observational study.

The case definition outlined by the CDC was used to define MIS-A[2] ;1) A severe illness requiring hospitalization in an adult ≥21 years; 2) A positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 3 months; 3) Severe dysfunction of ≥ 1 extra-pulmonary organ systems (hypotension or shock, cardiac dysfunction, arterial or venous thrombosis, thromboembolism, or acute liver injury); 4) Laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6); and 5) Absence of severe respiratory illness. Institutional review board approval was obtained.

Case 1

A woman in her 50's was admitted with unresponsiveness 6 days after recovery from COVID-19. Magnetic resonance imaging (MRI) showed multiple thalamic, cerebellar and left posterior cerebral artery territory infarctions. She was started on enoxaparin, Aspirin, and Levetiracetam. Her inflammatory markers were elevated (Table). On examination she was drowsy, febrile, had tachycardia, dense right hemiplegia, and bilateral extensor plantar responses. Multi-organ dysfunction was also identified. MR angiogram was normal. Echocardiogram and holter monitoring were normal. She was started on IV methylprednisolone 1gm/day for 5 days. Over the next few days, her platelet counts dropped to a nadir of 30 K/uL and she was started on plasmapheresis, and IVIg. She was transferred for rehabilitation after 2 months with residual aphasia and right hemiparesis.

Table 1. Shows the clinical and laboratory parameters of our patients with MIS-A

Serial number, Age (yrs), Sex	Underlying medical conditions	Time to onset after Covid-19 test negativity	Clinical signs and symptoms, Final Dx	Abnormal Laboratory parameters (peak)	Imaging	Treatment	Outcome and length of stay
1) 53/ Female	Hypertension	6 days after discharge from hospital. 16 days	Unresponsiveness, fever Right hemiplegia Mutism, Anasarca, Melena Oral mucositis.	Hb-7 gm ((12 – 15 gm/dl) Platelets- 70 (150-450 K/uL) TLC -26.4 (4-11 K/uL)	MRI brain - Acute infarcts in posterior circulation territory, involving both cerebellar	Aspirin IVMP, IVIG, Plasma exchange	Aphasia, right hemiparesis. mRS-5 LOS-39

			Acute left vertebral artery occlusion with posterior circulation artery-artery embolism, non-oliguric renal failure, acute hepatitis, Anemia, Thrombocytopenia	ALC- 0.6 (1-3 K/uL) ANC- 25.2 (2-7 K/uL) CRP-51 (< 5mg/L) D-dimer-8770 (< 500 ng/ml) Ferritin-1832 (20 - 250 ng/ml) Fibrinogen 530 (175 – 400 mg/dl) LDH-4042 (135 – 214 U/L) ALT-83 (< 34 U/L) AST-70 (< 31 U/L) Creatinine- 4.4 (0.6-1.1 mg/dl) ANCA- negative ANA- negative DCT - positive Blood/ Urine cultures – negative ECHO-Normal SARS-CoV-2 RT PCR negative	hemispheres, right middle cerebellar peduncle, vermis, right Hemi pons, bilateral thalamus, left occipital lobe & left occipitotemporal areas with hemorrhagic transformation. .		
2) 64/Male	Hypertension	COVID reinfection. Partial COVID-19 vaccination status (1st infection was 7 months earlier and 1st dose of vaccination was 1 month earlier)	Fever, Acute right hemiplegia, global aphasia Large vessel occlusion	TLC – 6.1 (4-11 K/uL) ALC- 0.9 (1-3 K/uL) ANC- 4.3 (2-7 K/uL) CRP- 280 (< 5mg/L) D-dimer-18060(< 500 ng/ml) Ferritin-1291 (20 - 250 ng/ml) Fibrinogen- 704 (175 – 400 mg/dl) LDH- 700 (135 – 214 U/L) ALP – 1823 (Creatinine-1.5 (0.6-1.1 mg/dl) ECHO-Normal CSF –TC 10 cells/cmm3, protein- 48 mg/dl, CSF-SARS-CoV-2 RT PCR negative SARS-CoV-2-RT PCR positive on day 5	CTA – occlusion of left ICA at origin, absent left PCA. MRI- multiple infarcts left PCA, left MCA, right frontal area, recanalized left PCA, persistently occluded left ICA from origin	Tenecteplase IV, Aspirin, Clopidogrel, Enoxaparin s/c 3% NaCl Levetiracetam	mRS-5 LOS-23

3) 27/Male	None	8 weeks	Fever Chest tightness and vomiting Tachycardia Tachypnoea Myo pericarditis Hepatitis Acute Kidney Injury Oligoarthritis 8 days later transverse myelitis.	TLC- 15.4 (4-11 K/uL) ALC- 1 (1-3 K/uL) CRP-20 (< 5mg/L) D-dimer-1881 (< 500 ng/ml) hS Troponin I - 25 (<13ng/mL) BNP 810 (<100 pg/ml) Ferritin-1107 (20 - 250 ng/ml) AST-157 (< 34 U/L) ALT-343 (< 31 U/L) Creatinine 2.24 (0.6-1.1 mg/dl) CPK-464 (25 – 170 U/L) CSF- TC 3 cells/cmm^3, Protein 30mg/dl., CSF-SARS-CoV-2 RT PCR negative ECHO- ECHO - RA/RV dilatation, Mild TR, IVC plethoric, mild pericardial effusion, good LV function. SARS-CoV-2 RT PCR negative on admission	CT chest; Moderate bilateral pleural effusion with passive atelectasis of basal segments of lower lobes. RV appears dilated with prominent main pulmonary artery. However no definite evidence of any thrombus or embolus within the PA. CT brain normal MRI brain- Normal MRI spine- hyperintensity involving the lower thoracic cord and conus	Oral Prednisolone 1 mg/ kg. Colchicine. Tablets IVMP.	LOS -57 days mRS -0
4) 62/ Female	None	Right hemiplegia, global aphasia at the onset. Presentation with a stroke. Hypotension requiring vasopressors.	Fever, dry cough, hypotension requiring Noradrenaline, left ICA occlusion	D-dimer –1300 (< 500 ng/ml) Fibrinogen-481 (175 – 400 mg/dl) Ferritin-600 (20 - 250 ng/ml) CRP-98 (< 5mg/L) SARS-CoV-2 RT PCR positive on day 2.	MRI- Large, acute left MCA territory infarct. MRA-thrombotic occlusion of left cervical ICA extending into the intracranial segments of left ICA and left MCA CT Thorax- Patchy subpleural ground-glass opacity with interlobular septal thickening predominantly involves bilateral upper lobes / lower lobes and inferior lingula. CO RADS 3. Cardiomegaly	Attempted mechanical thrombectomy. DSA-occlusion of left ICA at origin which was opened, with tandem with thrombus in the cavernous segment and due to tandem occlusion, which could not be retrieved.	LOS- 17 days mRS-4

					with enlarged left atrium and left ventricles. Prominent pulmonary veins were noted.		
5) 41/Male	None	COVID-19 infection	Unresponsiveness, fever Left MCA stroke, Left ICA occlusion Acute kidney injury Hypotension requiring vasopressors Rhabdomyolysis	CRP 112 (< 5mg/L) Creat –5.6 (0.6-1.1 mg/dl) LDH- 525 (135 – 214 U/L) ALC-0.9 (1-3 K/uL) CPK-49581 (25 – 170 U/L) D-Dimer- 8350 (< 500 ng/ml) Ferritin-1340 (20 - 250 ng/ml) Troponin –86.9 (< 13 ng/L) BNP- 347 (<100 pg//ml)	MRI –large left MCA infarct, Left ICA, MCA occlusion	Antiplatelets, mannitol, Dexamethasone	Death mRS-6 LOS- 12 days
6) 32/Male	None	Recent COVID-19 infection 12 days ago.	Fever, Aphasia, Left ICA embolic occlusion Left orbital infarction syndrome	D-dimer 960 (< 500 ng/ml) ALC – 0.6 SARS-CoV2 antibodies-positive.	CT- hyperdense Left MCA sign MRI – left MCA territory infarct Repeat CT day 2- left orbital muscle enlargement, proptosis Repeat MRI- left optic nerve / choroidal infarction. Enlarged orbital muscles, consistent with OIS	DSA- left ICA terminus occlusion, TICI 2a recanalization achieved, Decompressive craniectomy Dexamethasone	mRS-5 LOS-27
7) 41/ Male	Smoker	Partially vaccinated status (Covishield 1 dose 10 days earlier)	Fever, Cough Rt sided weakness at onset	LDH –613 D-dimer –2250 (< 500 ng/ml) ALT 129 ((< 34 U/L) AST 67 (< 31 U/L) ECHO- EF 55% (midly reduced) SARS-CoV2 RT-PCR positive on day 3.	CT brain- multiple infarcts, abnormal meningeal enhancement MRI brain- scattered micro and macro hemorrhages in the cerebellar and cerebral white matter. Scattered gyriform leptomeningeal enhancement	Low molecular weight hepain, Apixaban Dexamethasone	mRS- 1 LOS-20
8) 33/ Female	Congenital heart disease (tetralogy of fallot) operated in early childhood.	COVID-19 20 days earlier	Fever, left upper neck swelling, tachycardia, hypotension, delirium, Rhabdomyolysis, Critical illness myoneuropathy,	CRP 173 (< 5mg/L) Creat 2.4 (0.6-1.1 mg/dl) LDH- 2500 (135 – 214 U/L) ALC- 700 (1-3 K/uL)	MRI brain normal CT thorax- subsegmental pulmonary embolism, lower lobe fibrosis.	IVMP 2gm/ day x 3 days IVIG Hemodialysis Plasma exchange, SLED	Death LOS- 17

			Thrombotic microangiopathy	Platelets –5000 (150-450 K/uL) CPK- 8500 (25 – 170 U/L) D-Dimer- > 20,000 (< 500 ng/ml) Ferritin- 1523 (20 - 250 ng/ml) Troponin – 386.9 (< 13 ng/L) BNP- 378 (<100 pg//ml) NCS- Severe axonal motor-sensory polyneuropathy EMG- scattered denervation in distal lower limb muscles.			
9) 31 Male	None	COVID-19 one month earlier	Fever, abdominal pain, Hypotension, Multi-organ dysfunction, cervical lymphadenopathy, Proximal muscle weakness MIS-A induced inflammatory myositis	D-dimer 16400 (< 500 ng/ml) CPK 1,02,000 (25 – 170 U/L) LDH 734 (135 – 214 U/L) CRP 134 (< 5mg/L) Platelets 155 (150-450 K/uL) Ferritin 30, 577 (20 - 250 ng/ml) Troponin 420ng (< 13 ng/L) Procalcitonin 1.29 (<0.05 ug/L) ANA/ANCA/ Myositis profile negative Blood cultures negative	MRI brain normal PET CT- Extensive skeletal muscle uptake FDG uptake, LL >> UL. ECHO- mild LV dysfunction	IVIG IVMP Dexa Hemodialysis	MRS-4 LOS-25 days
10) 30 Male	Remote history of epilepsy	COVID-19 one month earlier	Status epilepticus, dense right hemiplegia, accelerated hypertension, acute kidney injury, myocarditis	D-dimer-9900 ng/ml CPK-33,000 U/L ESR-105 mm/hr CRP 98m/dl Ferritin,-6800 ng/ml AST 350 U/L, ALT 375 U/L, Total bilirubin 3mg/dL Creatinine 5 mg/dl CSF -normal Blood cultures negative	MRI brain -left complete hemispheric cortical cytotoxic edema, ECHO- mild LV dysfunction	Mechanical ventilation, Midazolam, propofol, Ketamine, IVIg, PLEX	MRS- 4 LOS 65 days

Abbreviations: TC- total WBC count, ALC- absolute lymphocyte count, DCT- direct Coomb's test, RV- right ventricle, MRA – Magnetic resonance angiogram, CO RADS- COVID-19 Reporting and Data System (CO-RADS), IVMP- IV methylprednisolone

mRS- modified rankin score, GCS-Glasgow coma scale, ONSD- optic nerve sheath diameter NCS- nerve conduction study, OIS- orbital infarction syndrome.

Case 2

A man in his 60's was admitted with acute right hemiplegia and aphasia (NIHSS score 24). At admission SARS-CoV2 RT-PCR was negative. He had a prior history of COVID-19 illness 6 months earlier. He had received 1 dose of inactivated COVID vaccine (COVAXIN™, Bharat Biotech) 1 month earlier (partially vaccinated status). CT angiogram (CTA) showed a left internal carotid artery (ICA) and left PCA occlusion. (Figure 1) He was administered IV Tenecteplase. The next day, CT brain showed large left midbrain, thalamic and occipital infarcts. On day 3 he developed fever and tachycardia. Inflammatory parameters were elevated (Table). On day 4, he was intubated for an MRI which showed new infarcts in the left middle cerebral artery (MCA) territory and right frontal area. On day 5, bronchoalveolar lavage obtained at the time of intubation was positive for SARS-CoV2 RT-PCR. He was diagnosed with post-vaccination (PV), COVID reinfection associated MIS-A [PV-MIS-A]. CSF showed mild pleocytosis and was negative for SARS-CoV2 RT-PCR. He stabilized with IVMP.

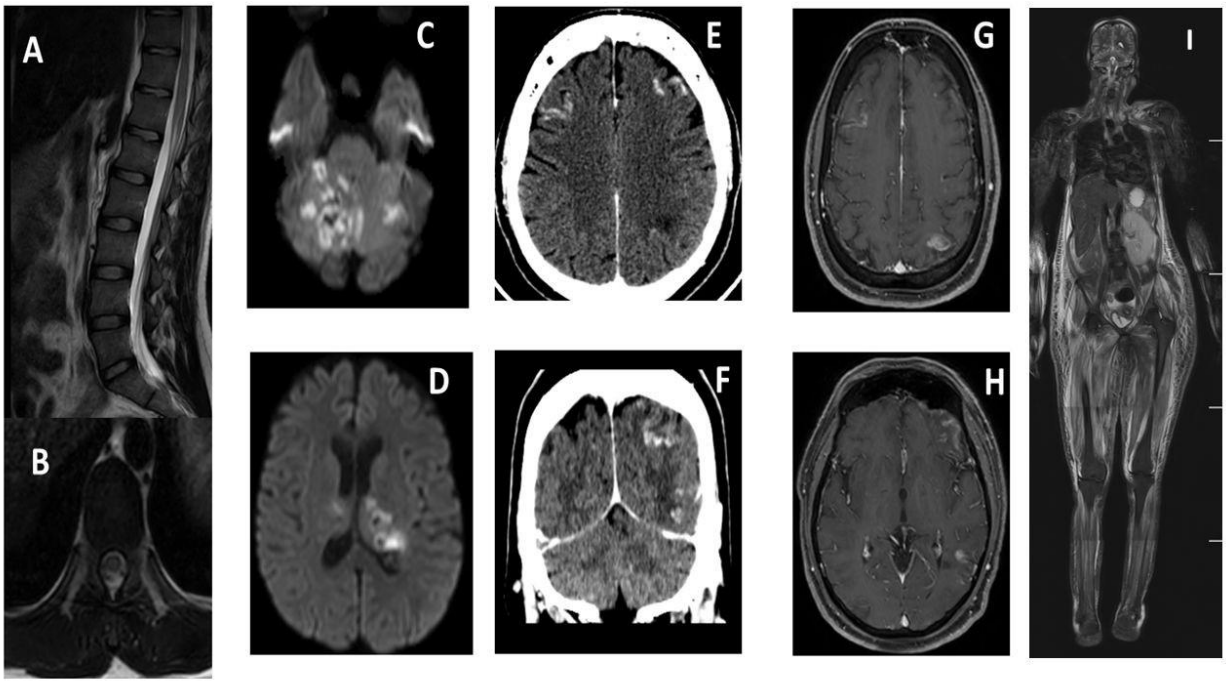

Figure 1. MRI images. Panel A and B: Sagittal and axial T2 weighted images of the lower spinal cord showing a subtle thoraco-lumbar cord hyperintensity. Panel C and D; Diffusion weighted MRI images showing scattered cerebellar and thalamic infarctions. Panel E and F; CT brain images showing cortical enhancement. Panel G and H. T1 post contrast axial images showing striking gyral contrast enhancement. Panel I- Whole body STIR muscle MR imaging diffuse hyperintensity involving the muscles and soft tissue of both upper limbs, neck, shoulder girdle, paraspinal region, chest wall, abdominal wall, pelvis and both lower limbs. Diffuse subcutaneous edema is noted in both lower limbs

Case 3

A man in his late 20's was admitted with chest pain, myalgia, fever, and vomiting, 8 weeks after COVID-19. On examination, he was febrile (39.5^{0}c), tachycardic, and tachypneic. Evaluation revealed myocarditis, pericarditis, hepatitis, and acute kidney injury. One week later, he developed difficulty in walking, urinary hesitancy, and paraesthesia in both feet. Examination revealed spasticity in his lower limbs (LL), reduced motor strength [2/5 in both LL], bilateral knee synovitis, exaggerated deep tendon reflexes and reduced touch sensations till the knees. MRI brain was normal but the spinal cord showed hyperintensities involving the lower thoracic cord and conus. (Figure 1) He was treated with 3 days of IVMP and completely recovery within 3 days.

Case 4

A woman in her 60's presented with a large left MCA stroke. Mechanical thrombectomy was

attempted with unsuccessful recanalization. SARS-CoV2 PCR was positive on day 2. She required vasopressor support for the next few days but slowly stabilized. At follow up 5 months later, she was aphasic (mRS-4). (Table 1)

Case 5

A man in his 40's presented with fever and unresponsiveness for 1 day. Evaluation revealed LVO. After admission he developed rhabdomyolysis, and acute kidney injury over the next 2 weeks and succumbed to multi-organ dysfunction. (Table 1).

Case 6

A man in his late 30's presented with recurrent fever after a 4 day asymptomatic period. 2 days later, he developed a right hemiplegia and aphasia. He was brought 15 hours after the onset and mechanical thrombectomy was attempted. In spite of TICI 2a revascularization, he worsened and developed complications such as an orbital infarction syndrome and worsening midline shift requiring decompressive craniectomy.

Case 7. A man in his 40's presented to the hospital with fever and right sided weakness. His inflammatory markers were elevated and CT brain showed subcortical hypodensities with gyral enhancement. SARS-CoV2 RT PCR was positive on day 3. MRI brain also showed striking gyral enhancement. CSF examination was normal and CSF SARS-CoV2 RTPCR was negative. COVID encephalitis was considered. He improved within 15 days of treatment with Dexamethasone, and antiplatelets.

Case 8

A woman in her 30's presented to us with fever, altered mental status and a tender mass at the angle of the left jaw. She had a history of COVID-19, 20 days earlier, which had been treated at home. On examination, she was delirious, febrile, tachycardic and had neck stiffness and diffuse cervical lymphadenopathy. MRI brain and CSF examination were normal. Echocardiogram and cardiac biomarkers were normal. She was started on antibiotics and IV methylprednisolone 1gm/day. She improved on day 2 but developed acute left ventricular failure and cardiogenic shock on day 3. After intubation, mechanical ventilation and inotropic support, she went on to develop atrial fibrillation, acute renal shutdown and acute liver failure, rhabdomyolysis and Critical illness myo-neuropathy by day 5. (Figure 2) She was treated with SLED (slow low efficiency dialysis) and IVIg 2gm/kg over 5 days. She developed refractory thrombocytopenia and succumbed on day 28.

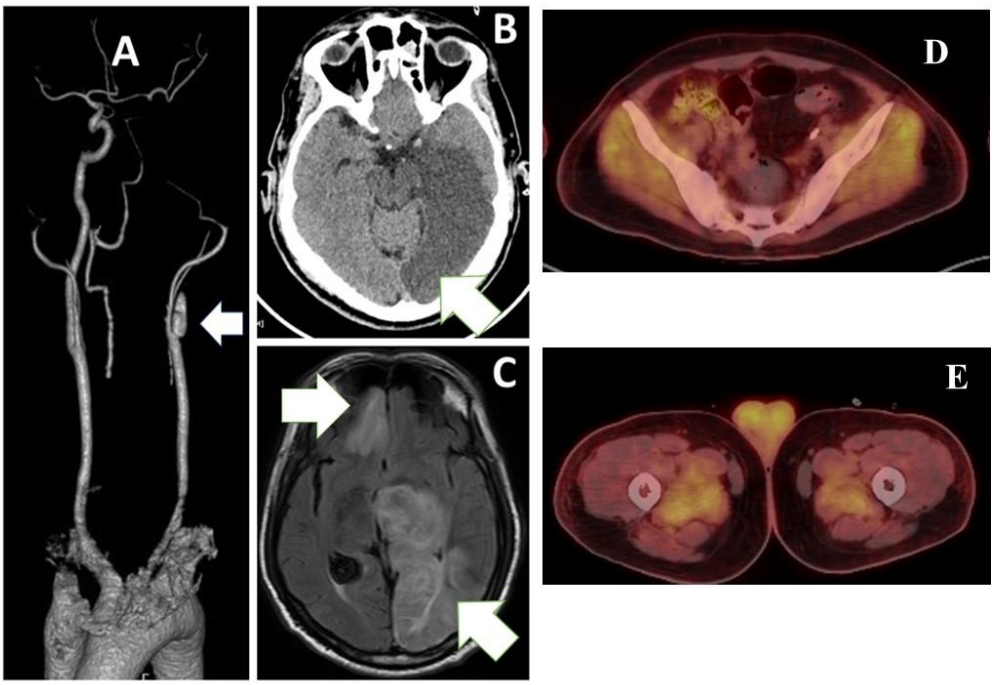

Figure 2. Panel A: CT angiogram shows a left ICA occlusion at the origin (White arrow). Panel B: CT brain on day 2 showing a left PCA territory infarction. Panel C: FLAIR MRI on day 5 showing a left thalamic, and occipital infarction along with a right frontal infarct. Panel D: FDG PET CT axial images showing gluteal muscle FDG avidity. Panel E: FDG PET CT axial images showing hamstring muscle FDG avidity.

Case 9

A 31-year-old man was admitted with fever, abdominal pain and shock. He had been referred as a case of pyelonephritis with septic shock. Further evaluation revealed multi-organ dysfunction with myocarditis and no evidence of urosepsis. He was started on antibiotics, IVIg, IVMP and hemodialysis. He continued to have a waxing and waning course. On day 18, he was noted to have severe proximal muscle weakness. CPK levels were over 1,00,000 U/L. 18 FDG-PET on day 23 showed diffuse skeletal muscle FDG uptake suggestive of an inflammatory myopathy. As he had fluctuating inflammatory markers, he was continued on high dose steroids, until clinical resolution

Case 10

A 30 year old man presented to us with Status epilepticus, dense right hemiplegia, accelerated hypertension, acute kidney injury and myocarditis. He required mechanical ventilation and intravenous anaesthetics for control of his status epilepticus. His MRI brain showed a unilateral (left sided hemispheric cortical cytotoxic edema) and ECHO showed mild LV dysfunction. He required prolonged rehabilitation and his mRS was 4 at the end of 2 months.

Results

Over a 22-month period, ten patients (1.1%) among 900 ICU admissions had MIS-A with severe neurological complications. The male: female ratio was 7:3 and the average age was 41 year (range 27-62). Six patients had no previous co-morbidities (66%), two were hypertensive and one was a smoker. Most patients were unvaccinated (80%). Two patients developed COVID-19 after partially vaccination with inactivated vaccines. 60% of patients had cardiac involvement requiring inotropic support and evidence of acute liver injury. 50% of patients had an acute kidney injury, 20% had dermatological manifestations. 50% of patients had lymphopenia (ALC < 1000/ cmm^3). Elevated thrombo-inflammatory parameters included D-Dimer - 6328 ng/ml (range 960-18060) [Normal < 500 ng/ml] and serum ferritin 4781 ng/ml (range 400-30,577) [normal -20 - 250 ng/ml]. D-dimer levels were elevated above 5 times the upper limit of normal in 80%.

CRP was elevated in 100% with an average range of 119 (32-280), platelet counts were 397,000 (range 30 -900 x K/uL), One patient developed severe pancytopenia with thrombocytopenia (30 K/uL), whereas one patient developed severe asymptomatic thrombocytosis (900 K/uL). 80% of patients required mechanical ventilatory support, IVIG was administered in 40% (4/10), IVMP in 8/10 (80%), and Plasmapheresis in 20% (2/10)

The severe neurological spectrum of MIS-A comprised of stroke with large vessel occlusion (LVO) in 40%, embolic stroke 10%, transverse myelitis (10%), COVID encephalitis (10%), rhabdomyolysis in 40%, rhabdomyolytic myopathy (20%), acute encephalopathy (20%) and status epilepticus (10%). (Figure 1 & 2) LVO was only partially recanalized in two patients due to severe vessel tortuosity or a lengthy clot. The mean time to diagnosis of MIS-A was 3 days (ranging from 1-7 days).

20% died due to multi-organ dysfunction syndrome (MODS). 60% had significant residual neurological impairment (mRS 4-6). Only 20% improved to baseline status.

Discussion

The case definitions for MIS-A are primarily intended for surveillance purposes and are preliminary definitions. Hence, it is important to recognize the heterogeneity and variable clinical spectrum of MIS-A. Delayed diagnosis, increasing severity of MIS-A, and severe neurological involvement increase mortality and morbidity.

MIS-A is a heterogeneous disorders with a variable clinical manifestations. Neurological manifestations are often overshadowed by cardiac or multi-organ dysfunction and are reported in around 23% of MIS-C.[6]

Our series demonstrates severe neurological manifestations of MIS-A in about 1% of ICU admissions during the COVID pandemic. The spectrum comprised ischemic strokes, transverse myelitis, COVID encephalitis, rhabdomyolysis, rhabdomyolytic myopathy, acute encephalopathy and status epilepticus. D-dimer, CRP, ferritin were the most frequently elevated laboratory markers. Lymphopenia was frequently encountered, and the median number of organ systems involved was 3.37 (range 1-5).

COVID-19 induces both a thrombocytopathy (functional platelet disorders affecting either platelet activity and/or function) and an endotheliopathy (functional endothelial disorders affecting either endothelial activity and/or function). The combination of these two leads to a thrombo-inflammation.[8] The SARS CoV-2 virus also impairs the immune system resulting in a T_h2 response against the virus rather than the essential T_h1 response. This excessive humoral

response with a diminished cellular immune response can lead to severe disease manifestations as well as a Type 3 hypersensitivity with deposition of immune complexes in blood vessels, complement activation and recruitment of other immune cells such as, producing a COVID microvasculitis.[9]

Ischemic strokes associated with COVID-19, are associated with hypercoagulability, vasculitis, thrombo-inflammation and cardiomyopathy.[10] Secondary hemorrhagic transformation of ischemic strokes may be due to endothelial damage or a consumption coagulopathy.[11]

The presence of ACE 2 receptors in the diaphragm may contribute to respiratory muscle weakness and longer duration of mechanical ventilation in COVID-19. Critical illness myopathy (CIM) and polyneuropathy (CIP) are also found in patients with severe COVID-19.[12] Factors such as medications, steroids, critical illness, muscle hypoperfusion and metabolic factors also contribute to CIM and CIP.[13,14] SARS-CoV-2 is also associated with an immune-mediated myopathy.[15] Whether similar mechanisms play a role in MIS-A are as yet unknown. Nevertheless, the para or post infectious hyper-inflammatory host response is likely to result in organ injury as in COVID-19. Thus, the neurological manifestations of MIS-A may mirror those seen in COVID-19, albeit with a lower frequency due to the rarity of this syndrome compared to the pandemic.

Severe neurological manifestations of post COVID MIS-A are rare (~1.1% of general ICU admissions) but comprise of varied manifestations. These patients, however patients experience greater morbidity and mortality than the general medical ICU patients or MIS-A patients with non-neurological manifestaions. In our cohort, around 80% of patients with severe neurological complications of MIS-A had a poor outcome.[16]

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