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Liaquat Ali
Hamad General Hospital, HMC, Doha Qatar,

Adnan Khan
Weill Cornell Medicine-Qatar, Doha, Qatar

Osama Elalamy
Hamad General Hospital, HMC, Doha Qatar

Beatriz Canibano
Hamad General Hospital, HMC, Doha Qatar

Mohammad Al hatou
Hamad General Hospital, HMC, Doha Qatar

See next page for additional authors

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Authors

Liaquat Ali, Adnan Khan, Osama Elalamy, Beatriz Canibano, Mohammad Al hatou, Ghulam Adeli, Islam Ahmed, Ambreen Iqrar, Ahmed Abdussalam, A Saif Ibrahim, and Sundus Sardar

A RARE PRESENTATION OF ACUTE FLACCID MYELITIS IN COVID-19 PATIENT: A CASE REPORT

Liaquat Ali[1], Adnan Khan[2], Osama Elalamy[1], Beatriz Canibano[1], Mohammad Al hatou[1], Ghulam Adeli[1], Islam Ahmed[3], Ambreen Iqrar[1], Ahmed Abdussalam[1], A Saif Ibrahim[1], Sundus Sardar [1]

[1.]Department of Neurology: Hamad General Hospital, HMC, Doha Qatar, [2.]Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar, [3.]Department of Radiology: Hamad General Hospital, HMC, Doha, Qatar

Correspondence to: *Liaquat Ali Hamad General Hospital, Neurology Dept HGH, al Rayyan road, PO box 3050, Doha, Qatar. Email: lali5@hamad.qa*

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Introduction: SARS-CoV-2 virus enters human cells via ACE-2 receptors and causes multiple organs dysfunction. These ACE-2 receptors are in cells surface of human lung, liver, heart, kidney and blood vessels. The expression of ACE2 receptors in cortical neurons, glial cells and spinal cord cells create nervous system susceptible to SARS-CoV-2 attack and may be a source of different neurological deficits including myelitis in COVID-19 patients.

Method: A 56-year old gentleman diagnosed with COVID-19 pneumonia presented with acute flaccid paralysis (AFM) of lower limbs, difficulty in sphincter control and urinary retention. MRI head was normal whilst thoracic spine with contrast demonstrated long continuous abnormal high signal intensity in the ventral horn of the grey matter in the upper and mid thoracic cord (T4 to T8) with no post contrast enhancement. Lumbar puncture showed CSF pleocytosis with lymphocytes predominance, high CSF protein and normal CSF sugar.

Result: Clinical presentation of patient, MRI of thoracic spine showed hyperintensity signals in ventral horn of gray matter and abnormal CSF analysis were suggestive of viral myelitis probable related to COVID-19 infection.

Discussion: Probable hypothesis that SARS-CoV-2 enters neuronal cells by ACE2 receptors, activation of immune system against virus and hyper-inflammatory response (cytokine storm) that damage blood - brain barrier (BBB) and enter central nervous system (CNS). Other probable hypothesis might be molecular mimicry of SARS-CoV2 and neuronal tissues. Another speculation that Corona viruses may invades peripheral nerves terminal then enter the CNS via a trans-synaptic transfer.

Key words: COVID-19, acute flaccid myelitis, SARS-CoV-2

BACKGROUND: COVID-19 pneumonia caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 virus) was first witnessed in Wuhan, China in December 2019. It has been confirmed that COVID-19 disease is caused by a new type of enveloped RNA coronavirus B named SARS-CoV-2. Studies have shown that the virus has 79% similarity with SARS virus [1]. SARS-CoV-2 virus enters the human body through ACE-2 receptors on the surface of human cells and causes disease. There are ACE-2 receptors in type II alveolar epithelial cells of human lung, so it has become the main target of SARS-CoV-2 in the pathogenesis of COVID-19 pneumonia [2]. It has been established that many critically ill patients have multiple organ dysfunctions including lungs, liver, heart, blood vessels and kidney. The expression of ACE2 receptors in cortical neurons and glial cell create them susceptible to a SARS-CoV-2 attack, which was the possible source of anosmia and other neurological deficits seen in COVID-19. ACE2 receptors are also expressed on the surface of spinal cord cells [3]. Probable one hypothesis is that infectious organism was targeted against by immunologic system which also attacked central nervous system tissue because of structural similarities between the corona virus cellular wall components and neuronal receptors (molecular mimicry) [4]. Another hypothesis is that ACE2 receptors were also expressed on the membrane of spinal cord neurons [5], suggesting that SARS-CoV-2 is implicated in AFM by ACE2 receptors on the surface of spinal cord neurons. Another speculation that Corona virus may invades peripheral nerves terminal then enter the CNS via a trans-synaptic transfer. AFM is a rare acquired spinal cord disorder that presents with the rapid onset of weakness in one or more limbs. There are diverse pathologies that affect the spinal cord including trauma, autoimmune, infectious, neoplastic, vascular and hereditary degenerative diseases. AFM is an estimated incidence of less than one case per one million populations in the United States [6]. Most cases in the United States have occurred in children with a median age of 6 years (range 3 months to 21 years). There have been also case reports of AFMoutside US including Canada and European countries. The true rate of AFM

among adults is not known, but it is thought to be extremely rare. There are numerous different pathologies can cause damage to anterior horn cells, the classic cause of AFP is by poliovirus, presenting as poliomyelitis. As polio has neared eradication via vaccination, there has been increasing recognition that other viruses may cause AFP, including enterovirus D68[7]. Acute motor weakness due to anterior horn cell involvement has been reported with many enterovirus serotypes. These include poliovirus and several nonpolio enteroviruses, such as enterovirus D68 and enterovirus A71, flaviviruses, West Nile virus and adenoviruses. These viruses target motor neurons in the brainstem and spinal cord. Furthermore, immune mediated causes of AFP have been identified (anti-myelin oligodendrocyte glycoprotein [MOG] antibody associated disease) that can be indistinguishable from virally mediated AFM. Standard testing of patients suspected of AFM includes magnetic resonance imaging (MRI) of the brain, cervical and thoracic spine with and without contrast, cerebrospinal fluid (CSF) analysis, nasopharyngeal swabs for viral testing (e.g., enterovirus PCR), fecal samples for viral testing (e.g. enteroviruses), and serum testing for potential mimics (e.g., anti-MOG antibodies). The diagnosis of AFM requires a clinical phenotype that includes acute flaccid weakness and MRI of the spinal cord that reveals predominantly gray matter involvement. We report a patient with COVID-19 pneumonia who suddenly developed AFP involving lower limbs and urinary retention after initial high fever and shortness of breathiness suggesting of AFP that could be attacked by SARS-CoV-2.

Case introduction:

A 56-year old gentleman, known of type 2 diabetes mellitus for 4 years and newly discovered with G6PD deficiency came to emergency department (ED) with complaints of high-grade fever of 38.9°C (102°F), fatigue for four days and lower limbs weakness and urinary retention for one days. Physician examination showed lower abdominal tenderness, palpable urinary bladder and bilateral lower limbs weakness. Urinary catheterization yields a urine volume more than 1200 ml, which not reveal any growth on culture. In ED ultrasound KUB requested to rule out obstructive uropathy that showed urinary bladder was distended, pre-void urine volume of 1327ml, post-void 873ml. Mild enlargement of prostate 24 ml. Chest X-ray (Fig: 2) showed bilateral infiltrates especially right lower zone and prominent broncho-vascular markings. Patient admitted on medical floor for evaluation for suspected COVID-19. After 12 hours of admission, patients developed short of breath, respiratory rate of 36 breaths/ minutes, SpO2- 92% on 5 liter/minutes on face mask oxygen. The test of COVID-19 RNA nasopharyngeal swabs PCR was positive; diagnosed with Covid-19 pneumonia. He was transferred to COVID-19 tertiary care Hospital for evaluation and treatment. Neurology team was consulted for evaluation of lower limbs weakness. Neurological examination showed normal higher mental function. Cranial nerves and extraocular movements were intact. Facial muscle strength was normal and equal bilaterally. Motor system examination of upper limbs were normal while lower limbs were low muscles tone, muscles strength of 3/5(MRC) distal and proximal bilaterally. Hyporeflexia at knee and ankle jerk with equivocal plantar responses. Sensation was intact to all modalities in the upper limbs. There was a subtle sensory level at T6 to pinprick testing. After admission, routine covid-19 laboratory test was requested. MRI Head was normal while cervical and thoracic spine with gad: (Fig:1a,b) showed continuous long subtle high signal intensity in the ventral horn of the grey matter in the upper and mid thoracic cord at T4-to T8 level (arrows in fig1a), with no post IV contrast enhancement; findings represent viral myelitis. Lumbar puncture was performed showed of CSF pleocytosis with lymphocyte predominance normal glucose and high protein as shown in Table 1. Patient's inflammatory markers were elevated as shown in table 1. Based on the clinical presentation, abnormal CSF and MRI thoracic spine, finding suggestive of acute flaccid viral myelitis most likely related to SARS-CoV-2 virus. Routine CSF cultures and PCR for viruses and bacteria were negative. Other viral panels like poliovirus, West Nile virus, Enterovirus, Zika virus did not performed due to financial constraint of patient. After diagnosis of COVID-19 pneumonia, standard treatment was given as local CDC recommendation except HCQ due to G6PD deficiency. Patient was treated for acute flaccid myelitis with pulse steroid and acyclovir according standard dosages. On the 4 day after admission, the patient found in room unresponsive, CPR started with initial rhythm was asystole, inj: epinephrine, atropine were given, return of spontaneous circulation (ROSC) achieved but patient was comatose, suspected unstable pulmonary embolism, empirical thrombolytic (rTPA) for unstable Pulmonary embolism (PE) was given, bedside "point of care" ultrasound (POCUS) exam showed signs of PE (+ve McConnell's Sign). Patient again went asystole, CPR done but patient ECG showed flat line and declared dead.

Discussion:

We present a rare case report of acute flaccid myelitis (AFM) in COVID-19 patient. Other similar case reported from Renmin Hospital of Wuhan University, Wuhan, China. Acute flaccid myelitis may be the one of rare neurological

manifestation of SARS-Cov2 virus. There was 36% neurological symptoms evidence in a one case series especially in more severe illness and higher mortality [8]. The neurological complications include acute ischemic or hemorrhagic stroke, impairment of consciousness, ataxia, seizures, skeletal muscle injury, meningitis, encephalopathy as well as Guillain Barre Syndrome. One of probable hypothesis that infectious organism was targeted against by immunologic system which also attacked CNS tissue because of structural similarities between the microbial cellular wall components and neuronal receptors result of "molecular mimicry" [4]. Another Probable hypothesis that corona virus may invade peripheral nerve terminals then access to the CNS via a synapse-connected route. The trans-synaptic transfer has been well documented for other CoVs, such as HEV-67 and avian bronchitis virus [9]. Neurons do have ACE2 receptors and postmortem pathological studies have detected SARS-Cov1 (by electron microscopy) in some neurons of patients with SARS-ARDS [10]. Recent study showed that SARS-CoV-2 could enter spinal cord neurons through ACE2 receptors on the membrane of spinal cord and causes acute myelitis. SARS-Cov2 activates of cytokines such as interleukin and TNF-alpha (cytokines storm) causes injury to the blood-brain barrier. With increasing damage to blood-brain barrier, cytokines penetrate the brain parenchyma [11]. With the penetration of blood content into the brain, viral particles can enter and damage neurons directly.

Conclusion:

This rare case report represents a patient with COVID-19 pneumonia associated with acute flaccid myelitis that was supported by abnormal MRI spinal cord and CSF findings. Acute flaccid myelitis might be very rear neurological manifestation of SARS-CoV-2 virus.

Table 1 Blood, biochemical and CSF investigations after admission:

Indicators(normal range)	Day- 1	Day-3	Day-4	Indicators(normal range)	Day-3
White blood cell (3.5-9.5×109 /L)	10.1	9.5	10.2	CSF WBC(0-5 /uL)	52
Neut/ANC(1.8-6.3×109 /L)	7.9	6.9	8	CSF –RBC	843
Lymphocyte (1.1-3.2×109 /L)	1.49	1.8	1.5	CSF- Neutrophils	4%
Hemoglobin (130-175g/L)	11.1	10.7	10.1	CSF -lymphocyte	89%
Platelets	369	265	223	CSF glucose(2.2-3.8mmol/L)	4.69
ALT (5-40U/L)	36	37	62 high	CSF protein(0.15-0.45 gm/L)	0.54
AST (8-40U/L)	30	63	125 high	S .glucose	6.7
S. total protein (60-83g/L)	73		66	CSF COVID 19 PCR	Negative
S.albumin (34-54g/L)	38		25 low	Gram stain/culture	No growth
Sodium	130	140	137	AFB stain/ culture	No growth
Creatinine (44-120umol/L)	110	63	61	MTB –PCR	Not detected

urea (3-9.2mmol/L)	5.2	4.5	5.7	**HSV PCR**	Not detected
D-Dimer(0.0- 0.49 mg/L FEU)		23.53 high		**CSF cryptoccocal antigen**	negative
CRP (0-5mg/L)	24		78 high	**S.HSV IgM/igG**	negative
Ferritin(30-553 ug/L)	271		435	**Blood culture**	No growth
Procalcitonin(0.5-2 ng/mL)	0.16		0.15	**Urine culture**	No growth
HbA1c		5.7		**COVID-19 PCR swab**	Positive
Vit B12			109 low		
TSH			0.47		
ANA			Negative		
ANCA			Negative		
Trop –T (3-15 ng/L)	30	63			
IL-6(≤ 7 pg/mL)			97 high		

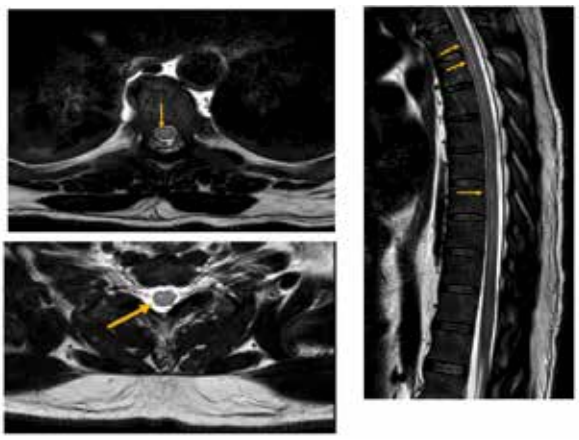

Fig 1a: Axial and sagittal T2 weighted images of MRI of the dorsal spine, demonstrate subtle continuous long high signal intensity in the ventral horn of the grey matter in the upper and mid thoracic cord at T4 to T8 level (arrows), with no post IV contrast enhancement; findings represent viral myelitis.

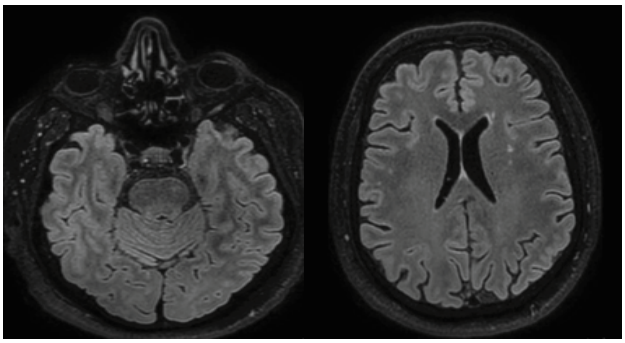

Fig 1b: Few tiny T2/FLAIR hyperintense foci are seen in the left frontal white matter, likely minor chronic microangiopathic changes.

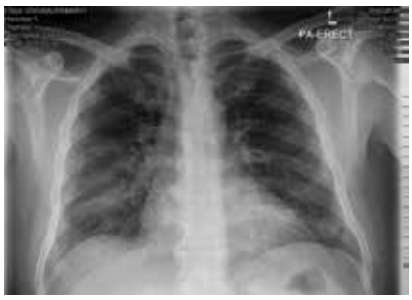

Fig 2: evolving infiltrates esp: right lower zone and prominent bronchovascular markings bilaterally.

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Adnan Khan; manuscript writing, manuscript review
Osama Elalamy; data analysis, manuscript writing and review
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Ghulam Adeli; manuscript writing, manuscript review
Islam Ahmed; data analysis, manuscript writing.
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