

Study of the Neurological Complications of COVID-19, a Cohort Study.

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ABSTRACT

Background: Middle East Respiratory Syndrome (MERS) has high pandemic potential and mortality. However, since its appearance in 2012, MERS neurological symptoms have rarely been reported. So, we aimed this study to determine the neurological complications among patients of Corona virus. Place and Duration: In the Department of Pulmonology, Neurology, ICU and Emergency department of Mayo Hospital Lahore for three months duration from March 2020 to May 2020. **Methods:** We assessed eight laboratory-approved MERS coronavirus infection (CoV) patients who exhibited neurological complications during treatment of MERS. These 8 patients belonged to a group of 35 patients managed in a given hospital during the 2019 epidemic in Pakistan. Clinical presentations, laboratory results and forecasts were defined.. **Results:** Eight out of 35 patients using MERS stated neurological manifestation after or during treatment of MERS-CoV. Possible diagnosis in these eight cases was encephalitis overlapping Guillain-Barré Bickerstaff syndrome, weakness attained in the ICU, or other infectious or toxic neuropathies. Neurological complications did not occur simultaneously with respiratory signs, but was appeared late after two to three weeks. **Conclusion:** During MERS treatment; neuromuscular complications are not uncommon and may have been formerly underdiagnosed. It is important to understand the neurological symptoms in an infectious disease like MERS because these signs are hardly assessed during management and may restrict the prognosis or need modifications in treatment.

Keywords: Middle East respiratory syndrome, Guillain-Barré syndrome, peripheral neuropathy, neurological complications.

INTRODUCTION

Since the emergence of the first respiratory syndrome in the Middle East (MERS) in Saudi Arabia in 2012, 1,830 cases approved by a laboratory in 27 countries have been documented, and 35.5% of these patients have died of this new disease.^[1,2] China experienced the largest MERS epidemic outside the Middle East, where thousands of patients were infected and died. MERS coronavirus (CoV) infected patients often has muscle pain, fever, shortness of breath and cough, which causes pneumonia. Though some infections are asymptomatic, severe symptoms occur in many cases that can lead to septic shock, multiple organ failure, acute respiratory distress syndrome (ARDS) and demise.^[3,4] MERS-CoV belongs to the genus Beta-coronavirus, whose species are identified as the potentially neuro-invasive. Though, there is currently miniature data on neurological symptoms and the occurrence of MERS. In Saudi Arabia, a retrospective study shows 26.2% of MERS infected cases had confusion and seizures in 8.6%. Four patients with acute CNS involvement (encephalitis, acute encephalomyelitis and stroke) and one patient with

critical polyneuropathy in patients with MERS have been reported.^[5-6] In this study, we define eight patients with neurological symptoms developing during MERS treatment at the hospital designed to treat MERS during the Pakistan epidemic in 2019.

MATERIALS AND METHODS

This study was held in the Department of Pulmonology, Neurology, ICU and Emergency department of Mayo Hospital Lahore for three months duration from March 2020 to May 2020. We examined retrospectively the laboratory, radiological results and clinical records of all patients infected with MERS-CoV. A total of 35 patients were selected for the study. Mayo Hospital is one of the leading isolation hospitals designed to treat critically ill MERS patients. Medical records of eight patients, especially those with neurological manifestations, were assessed in detail by 2 qualified neurologists. The MERS-CoV infection confirmation was done by applying reverse transcription polymerase chain reaction (RT-PCR) to lower respiratory tract samples (endotracheal aspirates and collected sputum) as recommended by the WHO. Conferring to the 3rd international consensus definition; Clinical stages of sepsis were defined for septic shock and sepsis. We determined the Simplified Acute Physiology Score II of all subjects in the intensive care unit (ICU). This

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analysis was accepted by the Corporate Ethics Committee.

RESULTS

During the study, 35 MERS-CoV infections confirmed in the laboratory were accepted. Virus transmission was related with health providing centers in all recognized patients. 50 days was the mean follow up time [interquartile range (IQR) = 15–300 days]. Of the 35 definite MERS-CoV subjects, 25 endured after antiviral agents treatment and providing maximum supportive maintenance. High doses of oral ribavirin [2000 mg loading dose, followed by 1200 mg every eight hours, then every 8–14 days, 600 mg / hour] and oral ritonavir/ lopinavir (400 mg / 100 mg every 12 hours for ten days), pegylated interferon alfa-2a given

subcutaneously (180 µg weekly for 14 days) were given to all infected subjects irrespective of the severity of the disease as per recommendations. The clinical results and demographic characteristics of all subjects are given in [Table 1]. Three people expired of late or early respiratory failure due to disease advancement.

The neurological complications among patients and its characteristics

Eight of the 35 registered patients (5 males and 3 females) presented with neurological manifestations after or during MERS-CoV treatment, and all subjects were referred for further management to a neurologist. 47 years was the average age of the patients (IQR = 28–48 years). The treatment given and clinical presentations in these eight patients are summarized in [Tables 2,3].

Table 1: ?

Variable	Value (n=32)
Sex, male	15(46.9)
Age, years	48(42-72)
Incubation period, days*	9(28.1)
Time from symptom onset to antiviral therapy, days	7(21.9)
Comorbid illness	14(43.8)
Diabetes mellitus	5(15.6)
Hypertension	2(6.3)
Chronic heart disease	1(3.1)
Chronic renal disease	2(6.3)
Bronchiectasis	2(6.3)
Malignancy†	2(6.3)
Psychiatric disorder	1(3.1)
Ankylosing spondylitis	2(6.3)
Symptoms during the disease course	
Fever≥38°C	15(46.9)
Cough/sputum	14(43.8)
Dyspnea	10(31.3)
Myalgia or arthralgia	8(25.0)
Headache	3(9.4)
Confusion	7(21.9)
Seizure	0 (0)
GI symptoms (nausea, vomiting, or diarrhea)	19(59.4)
Asymptomatic	0 (0)
Chest radiography abnormalities	32(100)
Outcomes	
Need for oxygen supply	12(37.5)
Need for high-flow nasal cannula	5(15.6)
Need for mechanical ventilation	8(25.0)
Need for ECMO	2(6.3)
Time from hospital admission to discharge of survivors, days	17(8-23)
In-hospital mortality	7(21.9)
Time from hospital admission to death of non-survivors, days, median (range)	18(56.3)

Table 2: ?

Column1	Patient 1,2	Patient 3,4,5	Patient 6,7	Patient 8
Sex/age, years	Female/55, 68/ Male	Female/43, 53/Male, 56/ Male	Male/47, 51/ Male	Female/40
Initial symptoms	Cough, dyspnea, and chest discomfort	Fever, myalgia, chills, cough, sputum, and headache	Fever, cough, dyspnea, and headache	Cough, sore throat, and fever
Incubation period, days	5–18	10	4	3
GI symptoms	-	Vomiting and nausea	diarrhea	-
Respiratory support	Mechanical ventilation	HFNC	5 L/min nasal oxygen	2 L/min nasal oxygen
Hospital course and treatment				
Sepsis severity*	Septic shock	Sepsis	Sepsis	Pneumonia
PSI	104	63	56	48

Antiviral regimen	IFN, Rb, and LR	IFN, Rb, and LR	IFN, Rb, and LR	IFN, Rb, and LR
SAPS II	74	37	42	30
IVIG treatment	Yes	No	No	No
Antibiotics used before onset of neurological symptoms	Ceftazidime, teicoplanin, meropenem, and moxifloxacin	-	-	-
Steroid treatment	No	No	No	No

Table 2:

Column1	Patient 1,2	Patient 3,4,5	Patient 6,7	Patient 8
Days after MERS onset	Unclear*	16	20	21
Neurological symptoms	Hypersomnolence and weakness in all four limbs	Tingling/pain in both hands and below the knees, and Weakness in both legs	Tingling in distal parts of both hands and feet	Tingling in both hands
Cranial nerves	Ptosis and ophthalmoplegia	Normal	Normal	Normal
Motor	Weakness in all four limbs	Proximal dominant weakness in both legs	Normal	Normal
Neurological examination				
Deep tendon reflex	Hyporeflexia in all four limbs	Hyporeflexia in both legs	Hyporeflexia in both legs	Normal
Sensory	Normal	Normal	Hyperesthesia in distal parts of all four limbs	Normal
Laboratory findings				
Cerebellar function	Limb ataxia	Normal	Normal	Normal
NCS	Normal	Normal	Normal	NA
CSF	Normal	NA	NA	NA
Peak serum creatine kinase, U/L	45	48	99	NA

Patient 1 and 2

A 55-year-old female and a 68-year-old man were tested for RT-PCR, which may have been exposed to MERS-CoV at home 5 to 18 days before presentation in the hospital. A positive result for MERS-CoV in sputum was detected. In the past, one had atrial fibrillation, diabetes, hypertension and second patient is a known case of chronic kidney disease and hypothyroidism. After hospitalization, both patients refused any clinical result, but chest X-rays showed poorly defined turbidity in both lower lungs.

A triple anti-virus program was available. On the second day, the hospital complained of shortness of breath, and breathing problems advanced very quickly. In addition to the treatment regimen; antimicrobial therapy was given. The mechanical ventilation was intubated on 10th hospital day. Acute respiratory failure was surveyed by septic shock, ARDS and multiple organ failure. The breath began to restore on 17th hospital day and at 29th HD; the mechanical ventilation was stopped. The patient persisted sleepy and showed eyelid dropping or both eyelids for up to 34 hours after stopping the sedative midazolam on 25th hospital day. Neurological analysis showed mild limb ataxia and comprehensive external ophthalmoplegia. There was a suspicion of weakness in all four limbs. No oropharyngeal, nystagmus, sensory changes or paralysis were perceived. In all limbs; Deep tendon reflexes were diminished. Magnetic resonance imaging (MRI) of the brain and CSF assessment was also normal encompassing normal CSF MERS-CoV RT-PCR assay.

The diffuse slow-wave activity was observed on the electroencephalogram. Non-specific results were obtained in laboratory tests, including tests that determined the levels of thiamine, glucose, ammonia, blood gas, creatinine and electrolyte imbalance at the inception of neurological manifestations. One patient was identified with Bickerstaff's encephalitis (BBE) coinciding with Guillain-Barré syndrome (GBS). Anti-GQ1b IgM / IgG and anti-GM1 IgM / IgG antibody titers were determined at 40th hospital day and all tests came normal. On 47th hospital day; nerve conduction studies were normal. Neurological complications proceed to normal on 30th HD and were completely treated with approximately HD 60 [Figure 1].

Patient 3, 4, 5

A 53-year and 56-year-old male and a 43-year-old woman who was identified as MERS-CoV infection on laboratory investigation were admitted in Mayo Hospital. It is supposed that all patients were infected with MERS-CoV in some other health care center ten days prior to commencement. There were no major medical problems, but initially they were associated with severe muscle pain, fever, chills, and headaches and coughing. After 10 days; the patient established gastrointestinal complications such as anorexia, vomiting and nausea. On 4th HD, acute respiratory failure advanced in the first 2 patients, and the flow proportion of oxygen from the high flow nasal cannula augmented from 1.0 to 60 l/min, which is the inspiratory oxygen fraction. Chest x-ray showed diffuse glass appearance on both sides and intensive consolidation. On 1st HD; triple antiviral

therapy was started in addition to other therapies included anti-inflammatory, NSAIDS and antitussive. The radiological and clinical outcomes instigated to progress at 6th hospital day and at 10th HD; oxygen therapy was stopped. After discharge (HD 10), both men felt hand and knee pain. They sensed weakness of their legs and they had trouble in walking independently for one km. Both patients experienced normal temperature, proprioception and vibration. The reflexes of deep tendons slightly decreased in both legs. The laboratory tests do not signpost the occurrence of infectious autoimmune diseases (excluding previous MERS infection). Creatinine kinase and electromyography, nerve conduction and potential test results were normal. CSF studies have not been conducted. At 17th day; Weakness started to improve after the beginning of primary neurological signs and significantly extinct after 55 days. Though, pain and tingling sensation in 4 distal limbs persisted till the last follow-up visit (about 7 months after the onset of symptoms). This subject was assumed to have GBS or weakness attained in the ICU.

Patient 6, 7

A 47- and 51-year-old male with a history of hypertension and pulmonary tuberculosis was included due after confirmation of MERS-CoV infection from the laboratory. Previously, they contacted MERS from other health care center. Fever, cough, chest discomfort, shortness of breath and additional stool loss occurred in one patient 4 days after this exposure. Chest x-ray showed the ground glass appearance in the left lung. A triple anti-viral management was given. No additional medicine that might source peripheral neuropathy were given. O₂ therapy was administered through the mouthpiece and augmented to five liter per minute after hospitalization. At 5th hospital day; Pneumonia started to heal 14 days after the start of corona signs and O₂ rehabilitation gradually decreased at 10th HD. During this time, the distal limbs of the feet and hands began to tingle. They refused sensory symptoms before hospitalization. The neurological evaluation showed normal mentality, muscle strength and cranial nerves. There was a decrease in temperature sensation in the affected spine, elbows and knees. The reflexes reduced in both knees, but in both upper limbs were found normal. Other neurological findings were insignificant. The quantitative sensory tests and nerve conduction studies results were within normal range. They must have toxic or infectious polyneuropathy, and after disappear six months; sensory symptoms improved.

Patient 8

A 40-year-old female advanced a sore throat, fever and cough 5 days after exposure to MERS patients in other hospital. Chest radiography showed the glass

appearance in both lungs. A triple anti-viral treatment was given. She stated tingling sensation in both hands about three weeks after respiratory symptoms. She rejected sensory symptoms before the hospitalization. For 4 months; sensory symptoms lasted. A neurological study found that muscle strength and cranial nerves were normal. The patient experienced a normal temperature, proprioception and vibration tests. Reflexes of four limbs were within normal range. The patient did not come for follow-up so that the nerve conduction studies were not done. She was identified with acute sensory neuropathy caused by an infection or toxin.

DISCUSSION

Eight MERS-CoV infection patients exhibited precise neurological symptoms in the course of treatment. These patients developed BBE, possibly coinciding with GBS, ICU-induced acute sensory neuropathy and weakness as a result of infection or toxin.^[7,8] A predominantly fascinating verdict was that nearly one in six MERS-CoV infected patient showed neurological manifestation after or during confirmation of the infection.^[9,10] Though statistics collected from one facility, this signifies a significant percentage of infested patients and proposes that such patients can be diagnosed too early.^[11] Patient 1, 2 showed ophthalmoplegia, hypersomnolence and feebleness of four limbs after severe viral infection, so it is necessary to distinguish amid different situations, counting Wernicke encephalopathy, GBS variant, polyneuropathy and elongated neuromuscular blockade due to critical illness / myopathy. We evaluated the GBS variant as a likely analysis because this patient had an infection, relatively symmetrical motor weakness, and a clinically rare single-phase course over 4 weeks. We have omitted many conditions that simulate BBE in this patient grounded on anamnesis, CSF results and brain MRI. Lack of laboratory results does not exclude the diagnosis of BBE.^[12] Wernicke was an important condition for the elimination of encephalopathy, as it often manifests itself in variable degrees by ophthalmoplegia, ataxia and encephalopathy. Though, we do not believe that Wernicke's encephalopathy occurred in patient 1 for numerous causes: 1) Wernicke's patient did not show any distinctive variations related with encephalopathy in MRI (especially in patients without alcohol abuse). In Wernicke's encephalopathy, complete ophthalmoplegia and eyelid ptosis observed in this subject are rare, deficiency of thiamine has not been established on laboratory investigations, and the patient was non-alcoholic and has no diet deficiency.^[13] Critical myopathy/ polyneuropathy in a single patient is common in intensive care patients, but polyneuropathy / myopathy is not considered a

patient in a critical patient 1. Weakness of limbs and eyes lasted almost 2 months, and this is due to the long-term use of neuromuscular blocking agent. Neurological problems usually recover completely within 14 days in subjects with long-term neuromuscular block. We assumed that 2nd patient had a weakness due to the intensive care unit or GBS. Acute sensory neuropathy is a possible diagnosis in patients 3 and 4, which may be the result of infection with toxins and / or drugs or viruses. These 2 patients were given pegylated interferon alfa-2a, lopinavir and ribavirin / ritonavir to treat MERS-CoV. Interferon alfa-2a infrequently causes peripheral neuropathy, and numerous analysis have shown difficulties related to vascular neuropathy, sensory neuropathy, GBS, autonomic neuropathy and chronic inflammatory degenerative polyneuropathy. CoV-19 is a group of virus-surrounded RNA viruses that includes the alpha-coronavirus and beta-coronavirus (including SARS and MERS-CoV).^[14] These viruses have neuro-invasive and neuro-trophic properties, and CoV RNA has been discovered in the CNS of patients with several neurological diseases. The SARS-CoV structure is almost same to MERS-CoV, and these 2 viruses have many clinical features. Neurological symptoms perceived in SARS patients appeared for the duration of the Taiwan epidemic.^[15] 4 patients with critical myopathy / polyneuropathy were identified, 29 of the other groups testified CNS involvement in ischemic stroke in patients with SARS. Patients with MERS-CoV infections are more likely to experience neurological complications like other CoVs.

CONCLUSION

As a result, we found eight patients have neurological complications during treatment of MERS. The most probable diagnoses are BBE, GBS (including its variant) as well as toxins and weakness induced by ICU (including drugs) or sensory neuropathy related to viral infection. It was particularly interesting that neurological complications did not occur with respiratory symptoms, but with a delay of 2-3 weeks. It is important to understand that neurological complications are not uncommon and may be delayed because patients with MERS-CoV infection may have difficulty contacting a neurologist during isolation, and these patients rarely carry out neurological assessments. In addition, some neurological complications interfere with prognosis and require appropriate GBS therapy, such as immunoglobulin or plasma-apheresis.

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