Neurological Complications during Treatment of Middle East Respiratory Syndrome

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Background and Purpose Middle East respiratory syndrome (MERS) has a high mortality rate and pandemic potential. However, the neurological manifestations of MERS have rarely been reported since it first emerged in 2012.

Methods We evaluated four patients with laboratory-confirmed MERS coronavirus (CoV) infections who showed neurological complications during MERS treatment. These 4 patients were from a cohort of 23 patients who were treated at a single designated hospital during the 2015 outbreak in the Republic of Korea. The clinical presentations, laboratory findings, and prognoses are described.

Results Four of the 23 admitted MERS patients reported neurological symptoms during or after MERS-CoV treatment. The potential diagnoses in these four cases included Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome, intensive-care-unit-acquired weakness, or other toxic or infectious neuropathies. Neurological complications did not appear concomitantly with respiratory symptoms, instead being delayed by 2−3 weeks.

Conclusions Neuromuscular complications are not rare during MERS treatment, and they may have previously been underdiagnosed. Understanding the neurological manifestations is important in an infectious disease such as MERS, because these symptoms are rarely evaluated thoroughly during treatment, and they may interfere with the prognosis or require treatment modification.

Key Words Guillain-Barré syndrome, Middle East respiratory syndrome, neurological complications, peripheral neuropathy.

INTRODUCTION

Since the first case of Middle East respiratory syndrome (MERS) was reported in Saudi Arabia in 2012, 1,826 laboratory-confirmed cases have been documented in 27 countries, and 35.5% of these patients have died from this novel virus.[1,2] In May 2015, the Republic of Korea suffered the largest outbreak of MERS outside of the Middle East, in which 186 patients were infected and 38 deaths were confirmed.[3]

Patients with MERS-coronavirus (CoV) infections typically exhibit fever, myalgia, cough, and dyspnea, which typically proceed to pneumonia. Although some infections are asymptomatic, many cases present with severe symptoms that can result in acute respiratory distress syndrome (ARDS), septic shock, multiorgan failure, and death.[4] MERS-CoV is in the *Betacoronavirus genus*, whose species are known to be potentially neuroinvasive.[5] However, very little information is currently available on the neurological manifestations of MERS and their incidence rates. A retrospective study in Saudi Arabia found that 25.7% of MERS patients developed confusion and 8.6% experienced a seizure.[6] Only four cases with central nervous system involvement (acute disseminated encephalomyelitis, stroke, and encephali-

tis) and one case with critical-illness polyneuropathy have been reported for patients with MERS.[7,8]

Here we describe four patients with neurological manifestations that developed while they were being treated for MERS at a single hospital designated to treat MERS during the 2015 outbreak in the Republic of Korea.

METHODS

We retrospectively reviewed the clinical records and laboratory and radiological findings of all laboratory-confirmed MERS-CoV-infected patients who were admitted to Seoul Medical Center (Korea), which was one of the main designated isolation hospitals for the treatment of patients with severe MERS during the Korean MERS outbreak in May and June 2015. Specifically, the medical records of the four patients who experienced neurological complications were evaluated in detail by two experienced neurologists.

The presence of MERS-CoV infection was confirmed by applying real-time reverse-transcription polymerase chain reactions (RT-PCR) to specimens from the lower respiratory tract (collected sputum and endotracheal aspirates) according to the recommendations of the World Health Organization.[9] Clinical stages of sepsis were defined according to the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[10] We calculated the Pneumonia Severity Index and the Simplified Acute Physiology Score II to identify the severity of pneumonia and the condition of each patient upon admission to the intensive care unit (ICU).[11,12] This study was approved by the Institutional Review Board of Seoul Medical Center (approval no. 2015-069).

RESULTS

Demographic features of all admitted patients with MERS

Twenty-three laboratory-confirmed MERS-CoV-infected patients were admitted during the study period. The virus transmission was associated with health-care facilities in all of the identified patients. The mean follow-up period was 49 days [interquartile range (IQR)=12−290 days]. Of the total 23 confirmed cases, 19 patients survived following treatment with a combination of antiviral agents and maximal supportive care. A triple antiviral treatment regimen comprising subcutaneous pegylated interferon alpha-2a (180 µg per week for 2 weeks), high-dose oral ribavirin [2,000 mg loading dose, followed by 1,200 mg every 8 h (q8h) for 4 days and then 600 mg q8h for 4−6 days], and oral lopinavir/ritonavir (400 mg/100 mg q12h for 10 days) was administered to all patients regardless of disease severity, which was in accordance with

the interim recommendations generated during the early period of the Korean MERS epidemic.[13] The demographic characteristics and clinical outcomes of all patients are presented in Table 1. Four patients died due to early or late respiratory failure caused by the progression of the disease.

Table 1. Demographic features of patients with laboratory-confirmed MERS coronavirus infection

Variable	Value (*n*=23)
Sex, male	14 (60.9)
Age, years	46 (39–69)
Incubation period, days*	7 (3–14)
Time from symptom onset to antiviral therapy, days	6 (2–8)
Comorbid illness	12 (52.2)
Diabetes mellitus	3 (13.0)
Hypertension	1 (4.3)
Chronic heart disease	2 (8.7)
Chronic renal disease	1 (4.3)
Bronchiectasis	1 (4.3)
Malignancy†	1 (4.3)
Psychiatric disorder	2 (8.7)
Ankylosing spondylitis	1 (4.3)
Symptoms during the disease course	
Fever≥38°C	13 (56.5)
Cough/sputum	17 (73.9)
Dyspnea	9 (39.1)
Myalgia or arthralgia	6 (26.9)
Headache	2 (8.7)
Confusion	5 (21.7)
Seizure	0 (0)
GI symptoms (nausea, vomiting, or diarrhea)	18 (78.3)
Asymptomatic	0 (0)
Chest radiography abnormalities	23 (100)
Outcomes	
Need for oxygen supply	9 (39.1)
Need for high-flow nasal cannula	3 (13.0)
Need for mechanical ventilation	5 (21.7)
Need for ECMO	1 (4.3)
Time from hospital admission to discharge of survivors, days	13 (5–17)
In-hospital mortality	4 (17.4)
Time from hospital admission to death of nonsurvivors, days, median (range)	13 (5–26)

Except where indicated otherwise, data are median (interquartile range) or *n* (%) values.
*Five patients with an obscure incubation period were not included in the calculation, †One of the patients had a malignancy, hepatocellular carcinoma.
ECMO: extracorporeal membrane oxygenation, GI: gastrointestinal, MERS: Middle East respiratory syndrome.

Characteristics of the patients with neurological complications

Four of the 23 included patients (2 men and 2 women) complained of neurological symptoms during or after MERS-CoV treatment, and all of these patients were referred to a neurologist. Their median age was 46 years (IQR=27−46 years). The clinical presentations of these four patients and the therapies applied to them are summarized in Tables 2 and 3.

Patient 1

A 55-year-old man who may have been exposed to MERS-CoV in a hospital or through household contact between 5 and 18 days prior to his presentation at our hospital was admitted because an RT-PCR of his sputum revealed positivity for MERS-CoV. He had a history of atrial fibrillation, diabetes mellitus, hypertension, chronic kidney disease, and hypothyroidism. At admission he denied any clinical symptoms,

Table 2. Clinical presentations of patients with MERS who experienced neurological complications, and the therapies applied to them

	Patient 1	Patient 2	Patient 3	Patient 4
Sex/age, years	Male/55	Female/43	Male/46	Female/38
Incubation period, days	5–18	10	4	3
Initial symptoms	Cough, dyspnea, and chest discomfort	Fever, myalgia, chills, cough, sputum, and headache	Fever, cough, dyspnea, and headache	Cough, sore throat, and fever
GI symptoms	–	Vomiting and nausea	diarrhea	–
Hospital course and treatment				
Respiratory support	Mechanical ventilation	HFNC	5 L/min nasal oxygen	2 L/min nasal oxygen
PSI	104	63	56	48
Sepsis severity*	Septic shock	Sepsis	Sepsis	Pneumonia
SAPS II	74	37	42	30
Antiviral regimen	IFN, Rb, and LR	IFN, Rb, and LR	IFN, Rb, and LR	IFN, Rb, and LR
Antibiotics used before onset of neurological symptoms	Ceftazidime, teicoplanin, meropenem, and moxifloxacin	–	–	–
IVIG treatment	Yes	No	No	No
Steroid treatment	No	No	No	No

*Sepsis is defined as life-threatening organ dysfunction from a dysregulated host reaction to an infection. Septic shock represents a subtype of sepsis that is accompanied by severe circulatory, cellular, and metabolic abnormalities that increase mortality.[10]
GI: gastrointestinal, HFNC: high-flow nasal cannula oxygen therapy, IFN: type 1 interferon, IVIG: intravenous immunoglobulin, LR: lopinavir/ritonavir, MERS: Middle East respiratory syndrome, PSI: Pneumonia Severity Index, Rb: ribavirin, SAPS II: Simplified Acute Physiology Score II.

Table 3. Neurological manifestations and laboratory findings in patients with laboratory-confirmed MERS

	Patient 1	Patient 2	Patient 3	Patient 4
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
Days after MERS onset	Unclear*	16	20	21
Neurological examination				
Cranial nerves	Ptosis and ophthalmoplegia	Normal	Normal	Normal
Motor	Weakness in all four limbs	Proximal dominant weakness in both legs	Normal	Normal
Sensory	Normal	Normal	Hypesthesia in distal parts of all four limbs	Normal
Deep tendon reflex	Hyporeflexia in all four limbs	Hyporeflexia in both legs	Hyporeflexia in both legs	Normal
Cerebellar function	Limb ataxia	Normal	Normal	Normal
Laboratory findings				
CSF	Normal	NA	NA	NA
NCS	Normal	Normal	Normal	NA
Peak serum creatine kinase, U/L	45	48	99	NA

*Neurological symptoms were detected 24 days after the initial onset of respiratory symptoms.
CSF: cerebrospinal fluid, MERS: Middle East respiratory syndrome, NA: not available, NCS: nerve conduction study.

but chest radiography revealed ill-defined opacities in both of his lower lungs.

A triple antiviral regimen was initiated. He began to complain of dyspnea on hospital day (HD) 2, and his respiratory deterioration then progressed very rapidly. Antimicrobial therapy was added to his treatment regimen. He was intubated, and a mechanical ventilator was added on HD 10. Acute respiratory failure was followed by ARDS, septic shock, and multiorgan dysfunction syndrome. His respiratory status began to improve on HD 16, and he was taken off the mechanical ventilator on HD 28. The patient remained drowsy and exhibited bilateral ptosis up to 31 h after the administration of the sedative midazolam was stopped on HD 25. A neurological examination revealed complete external ophthalmoplegia and mild limb ataxia. Weakness was also suspected in all four limbs [Medical Research Council (MRC) grade 4]. Nystagmus, sensory changes, and oropharyngeal or facial palsy were not observed. Deep tendon reflexes were decreased in all limbs. The results of brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies were normal, including a negative CSF MERS-CoV RT-PCR assay. An electroencephalogram exhibited diffuse slow-wave activity. Nonspecific results were obtained in laboratory studies performed at the onset of neurological symptoms, including in assays to determine the glucose, thiamine, blood gas, ammonia, electrolyte, and creatinine levels. He was diagnosed with Bickerstaff's encephalitis (BBE) overlapping with Guillain-Barré syndrome (GBS). IgM/IgG anti-GQ1b and IgM/IgG anti-GM1 antibody titers were analyzed on HD 39, and all were negative. The findings of nerve conduction studies performed on HD 46 were normal. His neurological complications began to improve on HD 30, and he had fully recovered by approximately HD 60 (Fig. 1).

Patient 2

A 43-year-old woman who had been diagnosed with a laboratory-confirmed MERS-CoV infection was referred to our hospital. It was suspected that she had had contact with MERS-CoV-infected patients in another hospital 10 days before the onset of her symptoms. No underlying medical problems were present, but she initially presented with severe myalgia, chills, fever, cough, and headache. After 1 week (HD 2), she developed gastrointestinal symptoms, including nausea, vomiting, and anorexia. On HD 3, she developed acute respiratory failure, and the flow rate of her high-flow nasal cannula oxygen therapy was increased to 60 L/min with an inspiratory fraction of oxygen of 1.0. A chest radiograph displayed bilateral diffuse ground-glass opacities and dense consolidation.

A triple antiviral regimen was initiated on HD 1, with other treatments only including antiemetic, antitussive, and nonsteroidal anti-inflammatory drugs. Her clinical and radiological findings began to improve on HD 5, and oxygen therapy was stopped on HD 10. On the date of discharge (HD 10), she described a stinging pain in both hands and below the knees. She felt that her legs were weakened, and she had difficulty walking for 1 km independently. A neurological examination revealed symmetric proximal dominant lower leg weakness, with her proximal and distal muscles at MRC grades 4– and 4, respectively. She experienced normal sensations to pinprick, temperature, vibration, and proprioception. Her deep tendon reflexes were mildly diminished in both legs. Laboratory findings did not indicate the presence of any underlying autoimmune, infectious (except for a previous MERS infection), or nutritional diseases. Her creatine kinase level and the results of nerve conduction, electromyography, and evoked potential studies were normal. A CSF study was not performed. Her weakness began to improve 17 days after the original onset of the neurological symptoms, and had largely disappeared
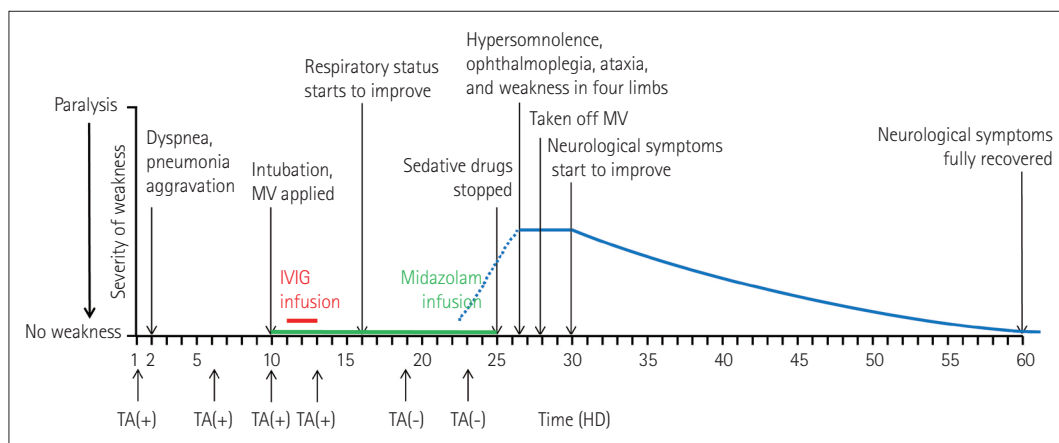

Fig. 1. Timeline of clinical events and virological results in patient 1. The onset of neurological symptoms and their course during the sedative state were uncertain, and are indicated by the dotted lines. HD: hospital day, IVIG: intravenous immunoglobulin, MV: mechanical ventilator, TA: tracheal aspirate.

after 53 days. However, tingling and pain in the four distal limbs continued until the last follow-up (approximately 7 months after symptom onset). This patient was presumed to have ICU-acquired weakness or GBS.

Patient 3

A 46-year-old man with hypertension and a history of pulmonary tuberculosis was admitted due to infection with laboratory-confirmed MERS-CoV. He had previously experienced contact with patients with MERS in another hospital. At 4 days after this exposure, he developed a fever, coughing, chest discomfort, dyspnea, and stool loss. A chest radiograph displayed ground-glass opacities in his left lung.

A triple antiviral regimen was initiated. No other drugs were administered that could cause peripheral neuropathy. Oxygen therapy was provided via a nasal prong and was increased to 5 L/min during admission. His pneumonia began to improve at 13 days after the onset of symptoms (HD 4), and the oxygen therapy was tapered off on HD 10. During this period he began to feel some tingling in the distal parts of his hands and feet. He denied experiencing any sensory symptoms prior to this admission. A neurological examination revealed normal mentation, cranial nerves, and muscle strength. He had bilateral decreases in pinprick and temperature sensations up to the knees and elbows. His reflexes were decreased at both knees but were normal in both upper extremities. His other neurological findings were unremarkable. The results of nerve conduction studies and quantitative sensory tests were normal. He was assumed to have infectious or toxic polyneuropathy, and his sensory symptoms gradually improved over 6 months.

Patient 4

A 38-year-old woman developed a cough, sore throat, and fever 3 days after being exposed to patients with MERS in another hospital. A chest radiograph exhibited diffuse ground-glass opacities in both lungs.

A triple antiviral regimen was started. She reported tingling in both hands at approximately 3 weeks after the onset of her respiratory symptoms. She denied experiencing any sensory symptoms prior to her most recent admission. These sensory symptoms lasted for more than 4 months. A neurological examination showed that her cranial nerves and muscle strength were normal. She experienced normal sensations in pinprick, temperature, vibration, and proprioception tests. Her reflexes were normal in all four extremities. A nerve conduction study was not performed because the patient was lost to follow-up. She was tentatively diagnosed with acute sensory neuropathy caused by a toxin or infection.

DISCUSSION

We have presented four patients with MERS-CoV infections who showed specific neurological manifestations during their treatment. These patients probably had BBE overlapping with GBS, ICU-acquired weakness, or acute sensory neuropathy that resulted from a toxin or infection. A particularly interesting finding was that almost one in five patients with MERS-CoV infections displayed neurological symptoms during or after the infection was confirmed. Although data were collected at a single institution, this represents a considerable proportion of infected patients, and suggests that such cases could have been underdiagnosed previously.

Patient 1 showed hypersomnolence, ophthalmoplegia, and weakness in all four limbs after a severe viral infection, and we therefore needed to differentiate between various conditions including GBS variant, Wernicke encephalopathy, prolonged neuromuscular blockade, and critical-illness polyneuropathy/myopathy. Because this patient had a preceding infection history, relative symmetric motor weakness, and a monophasic course with a clinical nadir within 4 weeks followed by a plateau, we considered GBS variant as a possible diagnosis.[14] BBE, one of the GBS variants, is considered a subtype of GQ1b antibody syndrome and is classically diagnosed based on its characteristic clinical features of progressive symmetric external ophthalmoplegia, ataxia, and impaired consciousness.[15] Because patient 1 had the classical triad of BBE accompanied by limb weakness, a diagnosis of BBE overlapping with GBS was suggested.[14] We excluded many BBE-mimicking conditions in this patient based on his clinical history, brain MRI, and CSF findings. The presence of antiganglioside antibodies and albuminocytologic dissociation in the CSF supported the diagnosis of BBE as part of the GBS spectrum. Nevertheless, a diagnosis of BBE is largely dependent on its clinical presentation. The absence of laboratory findings does not rule out a BBE diagnosis.[16]

Wernicke's encephalopathy was an important condition to eliminate in this patient because it also frequently manifests with varying degrees of encephalopathy, ophthalmoplegia, and ataxia. However, we considered it unlikely that Wernicke's encephalopathy was present in patient 1 for several reasons: 1) he showed none of the typical changes associated with Wernicke's encephalopathy in brain MRI, which has particularly high sensitivity (97−100%) in patients without alcohol abuse,[17] 2) the ptosis and complete ophthalmoplegia that were observed in this patient are rare in Wernicke's encephalopathy,[18] and 3) thiamine deficiency was not confirmed in laboratory tests and the patient did not have dietary deficiencies or alcoholism. Critical-illness polyneuropathy/myopathy appears frequently in ICU patients but was not thought

to be present in patient 1 because ophthalmoparesis and ptosis are very rare in critical-illness polyneuropathy/myopathy.[19] Prolonged neuromuscular blockade was another possible consideration in this clinical setting, but a neuromuscular blocking agent was not administered in patient 1. The limb and ocular weakness had lasted for almost 2 months, and this duration would be an unusual response to the prolonged administration of a neuromuscular blocking agent. Neurological signs typically completely recover within 1−2 weeks in patients with prolonged neuromuscular blockade.[19]

We hypothesized that patient 2 had ICU-acquired weakness or GBS. ICU-acquired weakness is diagnosed when a critically ill patient has limb weakness or ventilator dependency without heart or lung disease.[20] GBS was another possible diagnosis, since the patient experienced symmetric limb weakness following viral infection with a typical monophasic disease course.[14] These two diseases are differentiated by the presence of albuminocytologic dissociation in the CSF, positivity for antiganglioside antibodies, or demyelinating or axonal patterns in electrophysiology.[18,19] Patient 2 was evaluated neurologically after discharge, when her neurological symptoms had substantially improved; a lumbar puncture was therefore not performed, and critical information from laboratory studies was also not available. However, we cautiously supported a diagnosis of ICU-acquired weakness in patient 2, because a paraparetic presentation (as observed in this patient) is extremely rare in GBS and because dysautonomia and cranial nerve palsy, which frequently accompany GBS, were not observed in this patient.[18,21]

Acute sensory neuropathy was the probable diagnosis in patients 3 and 4, which may have resulted from a toxin and/or drug or viral infection. These two patients both received pegylated interferon alpha-2a, ribavirin, and lopinavir/ritonavir to treat MERS-CoV. Interferon alpha-2a rarely induces peripheral neuropathy,[22] and several studies have found complications associated with sensory neuropathy, vasculitic neuropathy, Bell's palsy, GBS, chronic inflammatory demyelinating polyneuropathy, and autonomic neuropathy.[23,24] Ribavirin is not associated with peripheral neuropathy,[24] while lopinavir/ritonavir is another possible causative drug. However, many people living with human immunodeficiency virus have been treated with this protease inhibitor for many years, and the risk of peripheral neuropathy in patients receiving lopinavir/ritonavir remains unclear.[25]

CoVs are a group of enveloped RNA viruses that include the *Alphacoronavirus* and *Betacoronavirus* [including MERS-CoV and severe acute respiratory syndrome (SARS) CoV] genera.[26] These viruses have neurotrophic and neuroinvasive characteristics, and CoV RNA has been detected in the central nervous systems of patients with various neurological diseases.[26,27] A recent *in vitro* study evaluated the human tissue tropism of MERS-CoV in diverse cell lines, and revealed that it has the ability to infect human neuronal cells (NT2).[28] The neuropathological effects of MERS-CoV infections are suggested to result from immune-mediated processes, either directly by viral invasion or via molecular changes that arise from systemic inflammatory response syndrome. The delayed onset of neurological complications, the absence of the virus in the CSF, and the development of GBS—which is one of the prototypical immunological diseases observed in our patients—might support the immunological mechanisms of these phenomena. This topic requires further microbiological and pathological studies.

The structure of SARS-CoV is very similar to that of MERS-CoV, and these two viruses share many clinical characteristics.[26] The neurological manifestations observed in patients with SARS were revealed during the Taiwan outbreak. Four patients who showed critical-illness polyneuropathy/myopathy have been described,[29] while other groups have also reported central nervous involvement in ischemic stroke in patients with SARS.[30] Patients with MERS-CoV infections have a high probability of experiencing neurological complications, similar to other CoVs.

In conclusion, we encountered four neurological manifestations during MERS treatment. The most likely diagnoses were GBS (including its variant), BBE, as well as ICU-acquired weakness and toxins (including drugs) or virus-related sensory neuropathy. It was particularly interesting that the neurological complications did not appear concomitantly with respiratory symptoms, instead being delayed by 2−3 weeks. Understanding that neurological complications are not rare and may be delayed is important because it might be difficult for patients with MERS-CoV infections to contact a neurologist while they are in isolation and because thorough neurological evaluations of these patients are rarely performed. Furthermore, some neurological complications interfere with the prognosis and require appropriate treatment, such as immunoglobulin or plasmapheresis for GBS.

Conflicts of Interest

The authors have no financial conflicts of interest.

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