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REVIEW

Middle East Respiratory Syndrome – What Every Otolaryngologist Should Know: A Review

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Abstract: In this study, we illustrate the history of Middle East respiratory syndrome corona virus (MERS-CoV) infection from the first reported case to the disease's outbreak and subsequent worldwide decline, with the aim of briefly defining the problem for the benefit of otolaryngologists. MERS-CoV belongs to the Coronaviridae family and causes a zoonotic disease, MERS, with strong camel to human and weak human to human transmission. The first documented case of MERS was reported in Saudi Arabia in June 2012. Viral replication produces inflammatory markers targeting T lymphocytes, with apoptosis being the end result. Nevertheless, the pathogenesis of this virus is not yet fully understood. The main symptomatic appearance is of mild lower respiratory tract infection with dyspnea and persistent cough in addition to systemic manifestations. The diagnosis is mainly based on the use of polymerase chain reaction for the detection of viral ribonucleic acid in the sputum or tracheal fluids. Otolaryngologic treatment mainly involves supportive adjuvant usage of interferon or antiviral drugs; however, approximately one-third of patients may not survive, and, therefore, otolaryngologists should be familiar with and remain mindful of the disease.

Keywords: MERS, coronavirus infections, zoonoses, lower respiratory tract infection

Introduction

Middle East respiratory syndrome (MERS), also known as camel flu, is a viral respiratory infection caused by the MERS-coronavirus (*MERS-CoV*),[1] a betacoronavirus derived from bats. Five beta-CoVs have jumped from animals to humans in the past 20 years and they include *HCoV-OC43, HCoV-HKU1*, severe acute respiratory syndrome coronavirus (*SARS-CoV*), Middle East respiratory syndrome coronavirus (*MERS-CoV*), and *SARS-CoV-2*.[2] H*CoV-229E, HCoV-OC43, HCoV-HKU1*, and *HCoV-NL63* usually cause mild symptoms, such as those of the common cold and/or diarrhea. In contrast, *SARS-CoV, MERS-CoV,* and the newly identified *SARS-CoV-2* are highly pathogenic, more commonly causing severe lower respiratory tract infection with a higher chance of developing acute respiratory distress syndrome and additional pulmonary manifestations.[3]

Symptoms may range from mild to severe and include fever, cough, diarrhea, and shortness of breath.[1,4] The disease presentation is typically more severe in patients with comorbid health problems. Approximately one-third of diagnosed patients do not survive.

Camels reportedly have antibodies to *MERS-CoV,* but the exact source of infection in camels remains undetermined. Moreover, camels are implicated in *MERS-CoV* spread to humans, but the mechanism is unclear.[3,4] Spread between

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humans typically requires close contact with an infected person. Its spread is uncommon outside hospitals. Thus, its risk to the global population is currently deemed to be fairly low.

As of 2019, there was no specific vaccine or treatment for the disease, although several antiviral medications have been studied.[1,5] The World Health Organization recommends that individuals who come in contact with camels should wash their hands frequently and should not touch sick camels and that camel-based food products should be appropriately cooked. Despite MERS' low risk to the global population, its high mortality rate necessitates that a thorough account of its characteristics should be readily available to every otolaryngologist; to our knowledge, this is currently lacking from the literature. In this review, we discuss the history, virology, and pathogenesis, epidemiology, transmission and symptomatology, and prevention and treatment of MERS ultimately aiming to contribute toward the prompt diagnosis and optimal management of this potentially fatal disease.

Observation

History

The first documented case of MERS, a zoonotic disease caused by *MERS-CoV*, was reported in Saudi Arabia in June 2012,[1] although the virus was named human coronavirus-EMC at that time by the Erasmus Medical Center in the Netherlands. The case was of an adult man admitted to the emergency department due to acute pneumonia and kidney injury.[4,5] In September 2012, a man from Qatar who had traveled to Saudi Arabia before the disease symptoms became obvious presented a similar clinical picture. Subsequently, a virological panel detected *MERS-CoV* infection in dromedary camels similar to that seen in the patient.[6,7] Cases of the disease have since been reported in the Middle East, North Africa, Europe, East Asia, and the United States of America.[8,9] Since September 2012, 2040 consecutive cases of MERS have been identified by the World Health Organization, with 712 deaths.[10,11]

Virology and Pathogenesis

MERS-CoV is a member of the Coronaviridae family of viruses.[3,12–15] It has a large RNA genome (26–33 kb) with a G+C content of 30–42%. MERS-CoV belongs to the 2C beta-coronavirus lineage in camels and humans.[4,15] This virus differs significantly from other beta-coronavirus, such as *SARS-CoV*, but has certain similarities with bat coronaviruses.[5,16] The functional receptor unit is dipeptidyl peptidase 4 (DPP4), and the expression of this receptor facilitates infection.[8,17,18] DPP4 can have extensive amino acid substitutions in different species. In humans, it is expressed in the lower respiratory tract, while in camels it is found in the upper respiratory tract.[9] This virus has the ability to infect multiple cell lineages, and although the epithelial respiratory cells are most susceptible to viral multiplication,[7] it is also seen in human macrophages, dendritic cells, and hepatocytes, as well as in the intestine and renal tubules. DPP4 is found mostly in type 1 and type 2 cells, alveolar macrophages, vascular endothelium, and plural mesothelia. Patients with preexisting lung conditions such as cystic fibrosis and chronic obstructive pulmonary disease exhibit increased expression of DPP4 receptors on the alveolar epithelium, which explains the increased morbidity and mortality due to MERS in preexisting respiratory diseases.[19]

Viral replication produces inflammatory markers targeting T lymphocytes, with apoptosis being the end result.[19] Nevertheless, the pathogenesis of this virus is not yet fully understood.

The innate immune system constitutes the primary line of defense against invading viruses. The pathogen-associated molecular patterns, represented by the viral RNA or double-strand RNA formed during viral replication, are recognized by intracellular sensors such as RIG-I and MDA5. After recognition, the downstream signaling cascade results in activation of NF-κB and IRF3 transcriptional activity.[20] This leads to the expression of type I interferon (IFN) and of pro-inflammatory cytokines, which constitute the defense line against viral infection at the early stage.[21] *SARS-CoV* and *MERS-CoV* have evolved several strategies to suppress the type I IFN response during invasion. SARS-CoV can interfere with the downstream signaling of the RNA sensors, including MAVS and TRAF3/6, directly or indirectly.[22]

As part of adaptive immunity, T cells play important roles in the primary defense line against coronaviruses. Studies have found that epitopes in the S protein[22,23] and the N protein of coronaviruses[24,25] can induce antibody responses in both mouse models and patients. IgM and IgG, produced by B lymphocytes, are formed after coronavirus infection.[26,27]

The virus can be detected in the sputum, tracheal aspirate, and bronchoalveolar tree lavage of symptomatic patients.[28] Polymerase chain reaction (PCR) analysis results have shown that the virus can be isolated from

nasal discharges during sneezing in asymptomatic patients up to 6 weeks before they become symptomatic. Contact with asymptomatic carriers is hazardous for otolaryngologists as well as for their other patients; therefore, otolaryngologists must take all possible precautions to avoid becoming infected. However, compared to animal-to-human transmission, human-to-human transmission is very limited.[29]

MERS-CoV can cause epidemic outbreaks in both humans and animals due to its ability to recombine, mutate, and infect different species. In vitro studies have shown that MERS-CoV has the ability to infect several types of non-human cells (bat, porcine, horse, etc.).[30,31] Indeed, recent studies have shown that the sequences of *MERS-CoVs* isolated from camels and human carriers are clustered together, contrary to the paraphyletic nature of bat *MERS-CoVs*. The genome-wide nucleotide substitution rate of the virus between the camel and human strains is 4.81×10^{-4} per site per year.[32]

MERS-CoV is acquired by camels less than 1 year of age[33] and produces asymptomatic manifestations or mild respiratory symptoms that are difficult to conclusively diagnose. For example, in 2013, a case was reported of a camel with fever and rhinorrhea.[34] In contrast, bats have the ability to carry the active form of the virus without detectable manifestations.[35]

Epidemiology

Most positive-stranded RNA viruses are known to trigger respiratory and enteric illnesses in animals (cattle, bats, mice, and horses) and in humans.[36,37] Four genera of human CoVs are known to be circulating globally and to be responsible for the common cold and the 2003 SARS outbreak. In 2012, two patients were infected with a novel type of virus. Both had traveled to, or were in, Saudi Arabia. Various cases were recorded thereafter, although 62% of cases with respiratory symptoms were not investigated for MERS, signifying that many cases could have been present and may have remained unnoticed. An initial outbreak of *MERS-CoV* was initially unnoticed in 2012 in the city of Al-Zarqa, Jordan, and was only retrospectively identified. Subsequent outbreaks were also detected in Yemen, Oman, Iran, Lebanon, Kuwait, the United Arab Emirates, and Saudi Arabia; these accounted for 85.8% of all reported cases. The rest of the cases were reported in the United Kingdom, Germany, Egypt, Italy, Malaysia, Greece, South Korea, the Netherlands, France, and the United States of America.[8,9] Most cases were either reported in the Middle East or had direct connection to a primary case of infection in the Middle East. Secondary local transmission following importation was documented in the United Kingdom, France, and Tunisia[2] (Figure 1).

In the Middle East, a significant number of cases were reported during March and April 2014, with a decline in mid-May of the same year. Across 16 hospitals, there were 186 confirmed cases in South Korea in May and June 2015. Similarly, in Lebanon, two cases were discovered in May 2014; the patient in the first case had persistent cough and dyspnea and tested positive for *MERS-CoV*. The patient denied any contact with animals or traveling overseas in the last 14 days. However, the patient had previously traveled to the Gulf region. In the second case, the patient was a 39-year-old male health-care worker involved in *MERS-CoV* surveillance in Saudi Arabia. The patient developed mild respiratory symptoms with positive serological tests for *MERS-CoV* after a negative result a month earlier.[38]

The virus appears to have an affinity for the male gender, as 64% of patients were men with a median age of 47 years, although the reason for this remains unknown. The mortality rate of patients was 35%.[1,7,13]

The exact mechanism underlying the seasonal pattern of viral infection between April and June is also not well understood. It has been hypothesized that it may be due to the camel birthing season, when there is intermingling of mature and young camels.[4]

Source and Transmission

Between 2010 and 2014,[1,4,39] the sera of cattle, goats, and sheep from various geographical areas of Saudi Arabia were analyzed for *MERS-CoV*, and all tests were negative. Similar studies were conducted in the United Arab Emirates, Jordan, and Spain, with similar seronegative findings. Dromedary camels were therefore believed to be the primary reservoir for *MERS-CoV*, and thereafter, a positive result was seen in a Qatar study.[40] Human-to-human transmission occurs between individuals in frequent and prolonged contact, within families, and as nosocomial infection. Animal-to-human transmission of *MERS-CoV* was seen in one case in Saudi Arabia, which resulted in the death of the patient.[41]

Symptomatology

The median incubation time of *MERS-CoV* is 5.2 days, although the duration may be up to 12 days (range, 4–14 days). Clinical manifestations are not distinguishable by

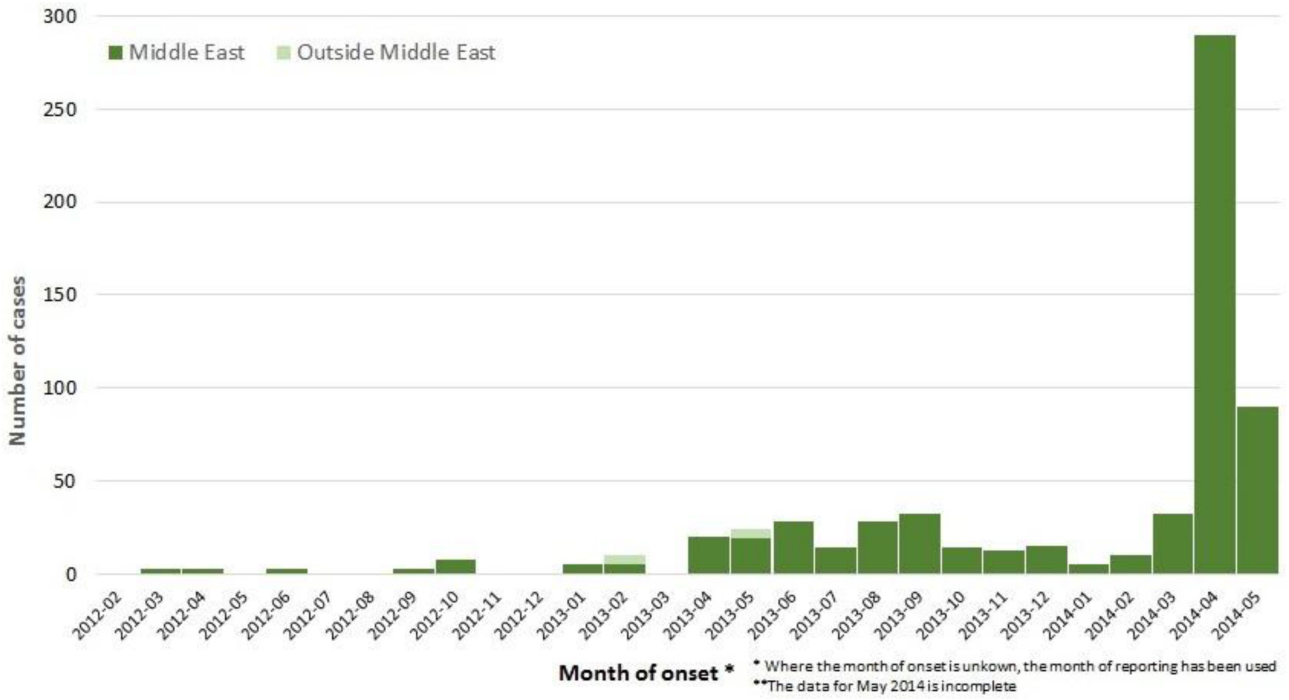

Figure 1 Distribution of confirmed cases of *MERS-CoV* by monthly onset and place of infection, March 2012–16 May 2014 (n=621).
Notes: Reprinted from European Centre for Disease Prevention and Control.[2]

otolaryngologists from other common and seasonal respiratory illnesses. The symptomatology ranges from no symptoms to an accelerated progression to death. Cases of intensive care unit (ICU) admission require approximately 5 days from onset, and these cases should be dealt with suspicion.[42] The otolaryngologist should inquire about travel and exposure to similar cases, which are important questions that can aid diagnosis. The key is recent travel to the Arabian Peninsula, to countries where dromedary camels are common, or to an area where there was a recent epidemic within 14 days.

Airborne infection isolation rooms are employed for isolating patients with suspected MERS. Air should be exchanged 12 times per hour, and personnel protection equipment (PPE) is required for safe contact with medical staff and physicians.[43] Care should be taken to remove the PPE without contact with contaminated outer surfaces.[8] The Scientific Advisory Board of Saudi Arabia has published the "Middle East Respiratory Syndrome Coronavirus; Guidelines for Healthcare Professionals" for protection and treatment guidelines, including chapters on personal and environmental preparation for patient isolation.[43]

Otolaryngologists should be aware that the possibility of mortality increases in the presence of the following factors: old age, immune disorders, comorbidities, malignancy, nosocomial infection, and end-organ diseases (pulmonary, cardiac, or renal).[44]

The initial presentation of MERS includes flulike symptoms such as fever, chills, rhinorrhea, fatigue, and myalgias. Respiratory symptoms, including cough and dyspnea, may become prominent later in the disease course. Pneumonitis is common. Gastrointestinal symptoms including nausea, diarrhea, and abdominal pain have also been reported.

From an otolaryngologic perspective, the physical examination findings associated with *MERS-CoV* infection are similar to those of any flulike illness, including fever, rhinorrhea (mostly clear), pulmonary findings such as hypoxemia, rhonchi, and rales (although some patients may have no abnormalities on auscultation), and tachycardia; hypotension may occur with severe illness, reflecting a systemic inflammatory response syndrome.

In more severe cases of MERS, patients with pneumonitis and acute respiratory failure develop severe hypoxemia and require mechanical ventilation and possibly oxygen rescue therapy such as extracorporeal membrane oxygenation. Vasopressor support and renal replacement therapy are often also required.

The symptomatic version of the clinical picture typically appears after an incubation period of 2–14 days. Confirmation of the diagnosis includes positive results for quantitative PCR targeting the viral envelope genes. Chest radiography may exhibit fibrosis, pleural thickening,

or a ground glass appearance. Other reported symptoms include fever, chills, myalgia, dyspnea, and cyanosis.[37]

Children and young adults usually have a mild course of the disease (fever, runny nose, and mild abdominal pain). Critical cases usually present with severe gastrointestinal manifestation, including nausea, vomiting, pain, and diarrhea, and acute kidney injury, which was reported in 50% of critical cases.[45–47] Severe progression may necessitate ICU admission with a 48-hour median time. The possibility of secondary bacterial infection has also been reported.[6] The recent pandemic of *SARS-CoV-2* necessitates differentiation of MERS from SARS-CoV-2 infection. Patients with MERS present with nonproductive cough (80 ± 5%), fever (77 ± 6%), sore throat (39 ± 11%), and diarrhea (10–20%), whereas the predominant symptoms of patients with Coronavirus disease 2019 (COVID-19) are fever (88.7%) and nonproductive cough (67.7%). Malaise, myalgia, dyspnea, expectoration, nausea, vomiting, dizziness, and headache are more commonly seen in patients with COVID-19.[48,49] (Table 1)

MERS may have high mortality of approximately 30–40% and lower infectivity, which has been measured by a basic reproductive number (R0) at approximately <1. Conversely, the R0 of *SARS-CoV-2* and *SARS* were found to be higher at 2.0–2.5 and 1.7–1.9, respectively.[47]

Table 1 Clinical Characteristics of MERS and COVID-19

	MERS[46–48]	COVID-19[49,56,57]
Year of emergence in the human population	2012	2019
Absolute number of cases		
Demographic and general characteristics	% of cases	
Signs and symptoms		
Fever	81.7–98	81–91
Cough	56.9–83	48–68
Dyspnea	22–72	19–31
Sore throat	9.1–14	29
Dizziness and confusion	5.4	22
Diarrhea	19.4–26	16
Nausea and vomiting	14–21	6
Complications	% of cases	
Intensive care unit admission	53–89	24
Acute respiratory distress syndrome	20–30	18–30
Acute kidney injury	41–50	3
In-hospital deaths	30–40	10–11

Abbreviations: MERS, Middle East respiratory syndrome; COVID-19, coronavirus disease 2019.

Treatment and Prevention

Up to the writing of this manuscript, no vaccination for *MERS-CoV* infection existed.[5] The main challenge is that animal models infected with the virus do not express the DPP4 receptor. Pharmaceutical companies do not appear to have sufficient monetary incentives to develop a vaccine at present, but if human-to-human transmission becomes more aggressive, the benefit of producing a vaccine will outweigh the cost.[7,12–14,50,51]

Early empirical antibiotic therapy is suggested in patients with suspected MERS, as other respiratory pathogens might also be contributing to pneumonia in hospitalized patients.

Supportive therapy, consisting of respiratory and circulatory support and monitoring of kidney function, is the main therapeutic intervention in the management of *MERS-CoV* pneumonia.[11]

When needed, hospitalized patients with severe MERS pneumonia also receive mechanical ventilation and vasopressor support and renal replacement and oxygen rescue therapy such as extracorporeal membrane oxygenation.[52]

In addition, interferon-α2b and ribavirin may decrease the viral load. These two drugs prohibited the multiplication of *MERS-CoV* in Vero and LLC-MK2 cells.[53,54] Thus, inhibitors of DPP4 may theoretically inhibit viral replication. Furthermore, the development of vaccines targeting the receptor binding subdomain of *MERS-CoV* is underway. Presently, a candidate DNA vaccine developed against *MERS-CoV* spike protein subunit 1 is under investigation in clinical trials.[43,54,55]

Conclusion

The otolaryngologic treatment of MERS mainly involves supportive adjuvant usage of interferon or antiviral drugs; however, approximately one-third of patients may not survive. Therefore, otolaryngologists should be familiar with and remain mindful of the disease.

Disclosure

The author reports no conflicts of interest in this work.

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