Japanese Journal of Infectious Diseases

Epidemiological and clinical characteristics of patients with Middle East respiratory syndrome coronavirus in Iran in 2014

Maysam Yousefi, Mohammad Moein Dehesh, and Mehrdad Farokhnia

Received: October 24, 2015. Accepted: March 22, 2016
Published online: May 9, 2016
DOI: 10.7883/yoken.JJID.2015.536

Epidemiological and clinical characteristics of patients with Middle East Respiratory syndrome Coronavirus in Iran in 2014

1. Maysam Yousefi; Assistant professor of infectious diseases, Department of internal medicine, Kerman university of medical sciences, Kerman, Iran
2. Mohammad Moein Dehesh*; Medical student, Iranian medical students association of Kerman local committee (IMSA), Kerman university of medical sciences, Kerman, Iran
3. Mehrdad Farokhnia; Assistant professor of infectious diseases, Department of internal medicine, Kerman university of medical sciences, Kerman, Iran

Running title: MERS-CoV in Iran

Keyword: MERS-CoV; Clinical Characteristics; Epidemiology; Iran, 2014

*Corresponding author: Mohammad Moein Dehesh; Student Research Committee, Deputy of Research and Technology at Kerman University of Medical Sciences, Ebn-e-Sina St, Tahmasbabad Junction, Shariaty St, Kerman, Iran.

Email:moeindehesh@gamil.com; Mobile: +98-913-349-4134

Summary

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was a great global concern in 2014. It has a wide range of manifestations that may differ in each area and also high mortality. In this study, we reported epidemiological characteristics, history, clinical and Paraclinical information of all five patients with laboratory-confirmed MERS-CoV from Iran. All these patients were from Kerman province. None of them had a history of travel, contact with animals or consumption of camel milk products but all of them had some sort of contact with a person who had been in Saudi-Arabia and experienced respiratory infection. One of the five patients was male and two of them passed away from the disease. Fever and respiratory symptoms were the most common symptoms and two patients had watery diarrhea. There were alveolar pattern in all available CXR's and elevated liver aminotransferases in three patients. Two of them had leucopenia and none of them had renal failure. In conclusion, we insist that all patients with acute respiratory symptoms, who had contact with a person that had recently traveled to Saudi-Arabia and experienced respiratory infection, should be investigated for MERS-CoV.

Cases

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was first diagnosed in a man with severe pneumonia in 2012 in Jeddah, Saudi Arabia. This man died of this new infectious disease (1). MERS-CoV has a very high mortality rate (2,3). Studies have indicated that this infection can present a wide range of respiratory and non-respiratory symptoms (4-9). Disease presentations may not start with respiratory symptoms. First MERS-CoV case in France was initially presented with abdominal pain and diarrhea (10). On the other hand a few MERS-CoV patients reportedly just had mild respiratory symptoms that did not need admission at all (11-13).

In this study we report epidemiological, demographical, and clinical characteristics of all five patients with MERS-CoV in Kerman province, Iran in 2014. Five patients with laboratory-confirmed MERS-CoV were reported from Iran including three citizens, one anesthesiologist and one nurse assistant.

We reviewed history, clinical manifestations, laboratory data and imaging of the three ordinary patients that were hospitalized in Afzalipoor hospital in Kerman-Iran and the nurse assistant. Demographic and epidemiologic characteristics of all patients were assessed too. Source of information was their medical documents including, patients' interviews or their families, and their infectious disease specialists. This study was approved by ethical committee of Kerman University of Medical Sciences and at baseline; all patients informed consent was obtained.

Throat swab specimens and sputum samples were collected and analyzed by using real-time reverse transcription PCR (RT-PCR) performed on the basis of a previously reported method by targeting the upstream E region and open reading frame 1b of the virus (14).

There were a total of five patients with laboratory-confirmed MERS-Cov disease in Iran from May to July 2014. All of them were from Kerman province, Iran and lived there. None of the five patients with laboratory-confirmed MERS-CoV had a history of travel and known history of being in contact with animals or consumption of raw camel milk products in 14 days prior to becoming ill.

Patient one was a 52 years old woman. She was referred to hospital on May 11th, 2014 and was admitted on the same day. She reported fever, productive cough, dyspnea both during physical activity and at rest, watery diarrhea, and loss of appetite from May 1, 2014 and a history of close contact with a woman who had Influenza like illness and had travelled to Saudi Arabia to perform Umrah. She had a history of Hypertension and had been under

losartan treatment. In physical examination she had a fever reaching 39.6 °C, blood pressure of 115/80 mm Hg, respiratory rate of 36 per minute; oxygen saturation of 85% with receiving oxygen (Mask, 8L/min) and 50% without receiving oxygen; and also bilateral coarse crackle was detected at the basis of her lungs.

She was admitted on the day of reference with the initial diagnosis of pneumonia. CXR was taken and bilateral alveolar infiltration in the basis of lungs was seen. Laboratory data showed Leucocyte count of 3900 with 79·3% neutrophils, normal urea and creatinine and elevated ALT and AST (table 1). ECG was normal. In the second day of admission, echocardiography was done and showed no abnormality.

With the initial diagnosis of community acquired pneumonia, azithromycin and ceftriaxone were prescribed for her. After 48 hours, antibiotics were changed to meropenem and vancomycine because patient's condition didn't improv. And also oseltamivir was started because of suspicion to influenza. Based on close contact with the suspicious patient, RT-PCR was done for coronavirus and influenza on nasopharyngeal swab and deep respiratory secretions at the day of admission. She was transmitted to intensive care unit (ICU) on May 14th, 2014 because of her life threatening respiratory symptoms. Bronchoscopy also was done on May 19th, 2014 and bronchial washing smear showed nothing significant. RT-PCR became positive for MERS-CoV on May 21, 2014. Her condition deteriorated and she died on May 29th, 2014 because of severe respiratory distress.

Patient two was a 50 years old woman who had close contact with her sister (first case discussed so far). She became ill on May 11th, 2014 presenting symptoms such as fever, watery diarrhea (3-4 times a day), and loss of appetite. From May 17th, 2014 productive cough and nausea were added. In this period levofloxacin was prescribed for her as outpatient therapy but her symptoms were not getting better. She was referred to the hospital and was

admitted on May 19th, 2014. She had a hysterectomy without any other past medical history. She had a temperature reaching 37.8 °C, blood pressure of 110/65 mm Hg, respiratory rate of 21, oxygen saturation of 90% without receiving oxygen; and also fine crackle was detected at basis of left lung.

Lab data on admission day showed normal renal function test and abnormal AST (table 1). CXR was done and there was consolidation in left lower lobe. Ceftriaxone, Azithromycin, oseltamivir were prescribed for this patient. She had close contact with his sister. So RT-PCR was done for coronavirus on nasopharyngeal swab and deep respiratory secretions on the second day of admission. It was positive. Her symptoms did not worsen, and she did not need ICU admission. Finally she was discharged on 30 May 2014 with stable condition.

Patient Three was the assistant nurse of the first case, a 35 years old woman working at ICU. She developed fever and a mild flu like illness on May 26th, 2014 followed by a productive cough on May 28th, 2014. She did not have vomiting or diarrhea and nothing special in her past history.

Based on her close contact with the first case, her throat swab taken on (May 26, 2014) with the impression of MERS-CoV was positive (May 31, 2014). All her lab data was normal (table1). She was advised to stay home and follow infection control precautions. She became asymptomatic on June 3, 2014.

Patient four was a 44 years old male, national health-care worker (HCW), anesthesiologist, resident of Kerman province, Iran. He developed mild symptoms of an influenza-like illness on June 6th, 2014. He was reported to have chronic heart disease. His condition deteriorated as he developed dyspnea and was admitted to hospital on June 17th, 2014. Specimens were collected on June 17th, 2014 and RT-PCR became negative for MERS-CoV on June 18th,

2014. His condition continued to deteriorate and he was transferred to ICU on June 19th, 2014. Additional specimens were collected that day and tested positive for MERS-CoV on June 20th, 2014.

He had close contact with a SARI (severe acute respiratory infection) patient during an intubation. This SARI patient had fever, productive cough, and dyspnea and was admitted to afzalipoor hospital on 17 may 2014. He had a history of travel to Saudi Arabia to perform Umrah between 5 and 15 May 2014. RT-PCR was done one time for influenza and MERS-CoV on 22 may 2014 but were negative. He was transmitted to ICU and was intubated because of severe respiratory distress on 26 May 2014. His condition deteriorated and he passed away on May 30th, 2014 because of severe respiratory distress.

Patient five was a 67 years old woman with history of Chronic Obstructive Pulmonary Disease (COPD) and was admitted to a hospital on June 6th, 2014 due to COPD exacerbation. She was discharged on June 14th, 2014 and her treatment was continued at home. She was in a stable condition until she developed severe acute respiratory symptoms and was readmitted to a hospital on June 25th, 2014. In the first admission, she had a close contact with a patient who had SARI. The daughter of this SARI patient had traveled to Saudi Arabia while having close contact and living with each other. But this SARI patient was not investigated for MERS-CoV.

Her symptoms first started on June 22, 2014 including fever, productive cough and mild hemoptysis, pleuretic chest pain, moderate to severe dyspnea, nightly sweat, loss of appetite, and loss of weight over the past month. She just had a history of COPD in her past medical history for 20 years. she had a fever reaching 38.9 °C, blood pressure of 110/80 mm Hg, respiratory rate of 32 times/minute, oxygen saturation of 92% with receiving oxygen (Nasal canula, 4L/min) and 88% without receiving oxygen. In her physical examination, there was

coarse crackle at basis of both lungs and high resonance bronchial sounds in the upper half of lungs. Lab data on admission day showed elevated AST (59), abnormal PT (14.3) and INR (1.2) (table 1). In CXR, consolidation was seen in left lower lobe and right middle lobe. Antibiotic therapy was started for her including meropenem and vancomycine. The patient didn't respond to antibiotics, and also she had a close contact with a suspected patient, so RT-PCR for MERS-CoV was done and oseltamivir was started.

Her respiratory symptoms got worse and the patient was intubated and transmitted to ICU. Afterwards the patient left the hospital with personal consent and went to a private hospital. Her condition deteriorated there, and she died because of severe respiratory distress on July 4th, 2014. The result of PCR confirmed MERS-CoV several days later.

In this report we described the epidemiological linking, demographic features and clinical progression of patients with MERS-CoV in Iran. We couldn't find any reason to describe why all of MERS-CoV patients were from Kerman province in Iran. None of them had history of travel and known history of being in contact with animals or consumption of raw camel milk products but all of them had contact with a confirmed MERS-CoV case or suspected one who had either negative RT-PCR or didn't visit a practitioner. All of these suspected cases had severe acute respiratory syndrome and had traveled to Saudi Arabia, except the daughter of SARI patient (suspected case of course) who had close contact with the fifth case. This person had traveled to Saudi Arabia but she didn't have any respiratory syndrome.

One of five patients was male (male: female ratio 0·2:1). Investigations in Saudi Arabia reported that 62-72% of MERS-CoV cases were male (15,16). In the other countries which had imported MERS-CoV disease, most of the patients were male (17,18).

Two of five MERS-CoV patients died (40% mortality rate). The mortality rate of MERS-CoV was different all over the world ranged from 22-100% (16,17,19,20). Saudi Arabia as

the most involved country, reported mortality rate of 60% for MERS-CoV (16). Both dead patients had medical comorbidity including HTN and COPD while the other three patients were otherwise healthy. Tunisia reported something like Iran. One of their three MERS-CoV cases died while having diabetes mellitus, but the other two patients did not have medical comorbidity and recovered without any complications (18). Saudi Arabia reported that just two of 47 MERS-CoV cases didn't have underlying medical comorbidity and steroids use. Malignant diseases, chronic lung disease and HTN were the most related comorbidities with death (16). It is also similar to our data.

All MERS-CoV cases had fever and productive cough. Dyspnea and loss of appetite were the next common symptoms and were seen in three patients. Two patients had watery diarrhea and one of them had also nausea. Similarly myalgia and pleuretic chest pain were seen in one of five cases. Studies reported fever and cough as most prevalent symptoms (16,21). Frequency of the other symptoms in Iran and Saudi Arabia was similar (16).

CXR of three MERS-CoV patients were available and all of them showed alveolar pattern (not shown). In France, one of MERS-CoV cases had upper right lobe consolidation but the other one had nothing in CXR (21). In Saudi Arabia all patients had abnormalities in CXR including increased bronchovascular marking, patchy infiltration, patchy to confluent air-space consolidation etc (16). Another study in Saudi Arabia reported interstitial infiltrates in all MERS-CoV cases (22). A study in Egypt was done in 12 MERS-CoV cases and showed five normal, five scattered patches of rather confluent airspace fillings within one or both lungs, and two large consolidation (23).

Laboratory data of four of the five MERS-CoV patients were available. Two patients had just elevated aspartate aminotransferase (AST). One patient had elevated alanine aminotransferase (ALT) and AST. The last one had normal ALT and AST. Studies from

France and Tunisia didn't report Liver tests but frequency of elevated ALT and AST in Saudi Arabia cases was 11% and 15% that was considerably less than Iran (16). One of our cases had prolonged PT and INR, and two of them had leucopenia. French MERS-CoV cases reported sever renal failure against our cases (21). None of five MERS cases in Iran had renal failure.

All two MERS-CoV cases in France and 98% of them in Saudi Arabia were admitted to ICU (16,21). Four of five cases (80%) in Iran also admitted to ICU. Tunisia had one ICU admission of three patients that was less than the others (18).

In conclusion, we insist that all patients with acute respiratory symptoms,with close contact with a person recently been to Saudi-Arabia and experienced respiratory infection, should be investigated for MERS-CoV. The most important point seems to be history taking, especially contact history.

Conflict of interest: None to declare

Acknowledgments: We appreciate dr. Mohammad Mahdi Gouya and dr. Ali Akbar Haghdoost due to their cooperation at various stages of implementing the plan. Furthermore, we thank Mrs A Amini zadeh, hygiene responsible of Afzalipour hospital and all the staff and medical students of infectious unit who collaborated to manage these patients. The assist from MERS patients and families of deceased is also thankworthy. We also appreciate Dr.Reza Fallah's role in language revising of this paper.

References

1.Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012; 367:1814–20.

2. Cauchemez S, Van Kerkhove MD, Riley S, et al. Transmission scenarios for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and how to tell them apart. Euro Surveill 2013; 18(24): pii=20503.

3. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) – update.27 March 2014. Available at: http://www.who.int/csr/don/2014_03_27_mers/en/ 2014.

4. AlBarrak AM, Stephens GM, Hewson R, et al. Recovery from severe novel coronavirus infection. Saudi Med J 2012;33:1265–69.

5. Memish ZA, Zumla AI, Al-Hakeem RF, et al. Family cluster of Middle East respiratory syndrome coronavirus infections. N Engl J Med 2013; 368: 2487–94.

6. Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med, 2013; published online June 19. DOI:10.1056/NEJMoa1306742.

7. Bermingham A, Chand MA, Brown CS, et al. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. Euro Surveill 2012;17:20290.

8. Mailles A, Blanckaert K, Chaud P, et al. First cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human transmission, France, May 2013. Euro Surveill 2013;18:20502.

9. Guery B, Poissy J, el Mansouf L, et al, and the MERS-CoV study group. Clinical features and viral diagnosis of two cases of infection with Middle East respiratory syndrome coronavirus: a report of nosocomial transmission. Lancet 2013:381:2265–72.

10. Mailles A, Blanckaert K, Chaud P, et al. First cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human transmission, France, May 2013. Euro Surveill 2013;18:20502.

11. European Centre for Disease Prevention and Control (ECDC). Epidemiological update: additional confi rmed cases of Middle East respiratory syndrome coronavirus (novel coronavirus) in France, Saudi Arabia, and Tunisia. May 23, 2013. Available at: http://www.ecdc.europa.eu/en/press/news/lists/news/ecdc_dispform.aspx?list=32e43ee8%2de

230%2d4424%2da783%2d85742124029a&id=921&rootfolder=%2fen%2fpress%2fnews%2flists (accessed July 5, 2013).
12. Health Protection Agency (HPA) UK Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. Euro Surveill 2013;18:20427.
13. ProMED-mail. MERS-CoV—Eastern Mediterranean (07): Tunisia ex Saudi Arabia/Qatar, fatal, WHO. May 22, 2013. Available at: http://www.promedmail.org/direct.php?id=20130522.1730663 (accessed July 18, 2013).
14. Corman VM, Eckerle I, Bleicker T, et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill 2012;17(39):20285.
15. Ibrahim G Alghamdi, Issam I Hussain, Shaia S Almalki, et al. The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. International Journal of General Medicine 2014;7:417–423.
16. Abdullah Assiri, Jaffar A Al-Tawfi, Abdullah A Al-Rabeeah, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. The LANCET, 2013; Published online July 26. http://dx.doi.org/10.1016/S1473-3099(13)70204-4.
17. Helen Lucy Thomas, Hongxin Zhao, Helen K. Green, et al. Enhanced MERS Coronavirus Surveillance of Travelers from the Middle East to England. Emerging Infectious Diseases 2014;20(9):1562-1564.
18. Fekri Abroug, Amine Slim, Lamia Ouanes-Besbes, et al. Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections, Tunisia, 2013. Emerging Infectious Diseases 2014;20(9):1527-1530.
19. Maimuna S. Majumder, Sheryl A. Kluberg, Sumiko R. Mekaru, John S. Brownstein. Mortality Risk Factors for Middle East Respiratory Syndrome Outbreak, South Korea, 2015. Emerging Infectious Diseases 2015;21(11):2088-90.
20. Hamid Y Hussain. Incidence and Mortality Rate of “Middle East Respiratory Syndrome" -Corona Virus (MERS-Cov), Threatens and Opportunities. J Mycobac Dis 2014;4: 162. doi:10.4172/2161-1068.1000162.
21. Benoit Guery, Julien Poissy, Loubna el Mansouf, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. The Lancet 2013;381:2265–72.

22. Jaffar A. Al-Tawfiq, Kareem Hinedi, Jihad Ghandour et al. Middle East Respiratory Syndrome Coronavirus: A Case-Control Study of Hospitalized Patients. Clin Infect Dis 2014 Apr 9:ciu226.
23. Ahmed Hamimi. MERS-CoV: Middle East respiratory syndrome corona virus: Can radiology be of help? Initial single center experience. The Egyptian Journal of Radiology and Nuclear Medicine 2016;47(1) 95–106.

Table 1: Laboratory data of the cases

	First case	Second case	Third case	Fifth case	Normal range
Date of blood testing	May 11 Admission day 10^{th} day after first symptoms	May 19 Admission day 8^{th} day after first symptoms	May 26 Was not admitted Beginning of symptom	June 25 Admission day 3^{th} day after first symptoms	
Blood Cells					
Leucocyte count (cells per µL)	$3{\cdot}6 * 10^3$	$3{\cdot}8 * 10^3$	$4 * 10^3$	$7{\cdot}7 * 10^3$	$4\text{-}10 * 10^3$
Neutrophils (%)	79·3%	53·5%	64·3%	81·6%	23-45
Lymphocytes (%)	18·5%	37·3%	33·5%	8·1%	35-65
Hemoglobin (mg/dl)	11·9	11·6	13	14·1	11.5 – 16.5
Platelet (cells per µL)	$155 * 10^3$	$124 * 10^3$	$253* 10^3$	$117 * 10^3$	$150–450 * 10^3$
Blood Biochemistry					
Blood urea nitrogen (mmol/L)	15	15	21	30	17 - 53
Creatinine (µmol/L)	0.8	0·7	0·8	0·8	0·5 – 1·6
Alanine aminotransferase (U/L)	59	27	40	17	5 – 40
Aspartate aminotransferase (U/L)	101	60	23	59	5 – 40
Prothombin time (sec)	13	-	-	14·3	
INR (sec)	1	-	-	1·2	
Blood sugar (mg/dl)	109	167	167	108	<140
RT-PCR					
Date of sample collection	May 14	May 20	May 26	May 28	
Type of specimen samples	Throat swab	Throat swab	Throat swab	Throat swab	
Underlying Disease	Hypertension	None	None	COPD	