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Review Article

Middle East Respiratory Syndrome: An Overview

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ABSTRACT

Coronavirology has been progressing from the time it was first identified. They are known to cause mild respiratory and digestive tract infections in man, other mammals and birds. But with the advent of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) they have now evolved as a cause of severe respiratory illness with high fatality rate. The diversity of the corona virus is due to the presence of large genome, which can undergo recombination and the S1 domain of the spike glycoprotein is poorly conserved and hence can breach the cell type, tissue and host species barrier with relative ease. MERS-CoV is named by the coronavirus study group and it belongs to the C-lineage of Genus Betacoronavirus along with other bat coronavirus HKU4 and HKU5. The source and mode of transmission is not fully understood. Dromedary camels are suspected to be the primary source followed by other mammals such as bats, sheeps, goats etc. The majority of the secondary cases were reported among the healthcare workers. Till date no effective treatment or vaccine is available.

Since the first reported case of MERS-CoV, the numbers of cases have been increasing every year and will continue to rise. Therefore, implementation of appropriate preventive measures is very crucial in controlling the spread of the infection. Much awareness is needed to be created among the high risk groups such as the hospital staff, patient attendants and the general population regarding the possible sources, modes of transmission and preventive measures. Continuous vigilance and surveillance to identify new cases is essential. And more research is needed to study the evolution of coronaviruses.

Key words: Middle East respiratory syndrome, MERS, MERS-CoV, Corona virus.

INTRODUCTION

Corona virus was first identified in the 1960s and is recognized causes of mild respiratory tract infections in humans. [1] It is only in 2003 it caused infections in more severe form leading to 8,422 infected cases and 916 deaths worldwide, with case fatality rate of 10%. It was then named as severe respiratory syndrome corona virus. The epidemic had lasted for few months and eventually took a pandemic form involving many countries. [2,3]

In June 2012 a novel corona virus was detected in a patient from Jeddah, Saudi Arabia, who died due to development of progressive respiratory and renal failure. [4-6] This new corona virus did not resemble any of the five corona viruses known to cause

infection in humans previously such as HCoV-229E, -OC43, -NL63, -HKU1 and SARS. [7] This corona virus was named as the Human corona virus- Erasmus Medical Center (HCoV-EMC), as it was first isolated in Erasmus medical center, Netherlands. In September 2012 similar type of virus named ,Human corona virus England I was isolated from Qatari patient with respiratory illness who was transferred from Qatar to London, UK. [5] The isolated viruses from Saudi and the Qatari cases were 99.5% identical. [6] Subsequently, the virus was designated as Middle East Respiratory Syndrome Corona virus (MERS-CoV) by the corona virus study group. [5,6] Retrospective analysis of stored samples of a cluster of pneumonia cases in health care workers dating back to April 2012 confirmed MERS-CoV as the cause of the outbreak. [3,5 ,6]

EPIDEMIOLOGY

As of 5 February 2015, 971 laboratory confirmed cases of MERSCoV have been reported to WHO, including 356 deaths. [8] And community onset MERS-CoV cases continue to occur. [6] The majority of the cases (>85%) have been reported from Saudi Arabia. The affected countries in the middle east include Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen; In Africa: Algeria, and Tunisia; in Europe: Austria, France, Germany, Greece, Italy, the Netherlands, Turkey and the United Kingdom; in Asia: Malaysia and Philippines. [8]

Occurrence of new cases seem to follow a seasonal pattern, with number of cases rising from March-April, and the majority of cases are seen during the mid-March every year. This also coincides with the camel birthing season. [6,9] Up to 75% of the cases reported were secondary cases that are infection is acquired from another infected person. [9] The majority of secondary cases were seen in the Health care workers. [6,9] Largest cluster of cases to date occurred in a health care facility in Al-Hasa, Saudi Arabia. [10] Only very few instances of transmission with in household have been reported. [6,9] Incubation period ranges from 2-14 days. [3,9,11] Patients are not infectious during incubation period. Period of infectivity is unknown. [9] But a contact investigation done in German Hospital, ruled out transmission to contacts after illness day 20. [12] Also asymptomatic cases may not be contagious. [9]

Also source of MERS-CoV and the mechanism of transmission are not fully understood. It is suggested that source could be zoonotic in origin. [13] Dromedary camels (Camelus dromedairus) are suspected to be the primary source of infection for humans. [6,9] Serological studies conducted in dromedary camels from several countries that reported MERS cases revealed widespread prevalence of MERS-CoV specific antibodies in them. [14] MERS-CoV isolated from the patient from Saudi Arabia was 100% identical to the virus isolated from camel from the same patients camel farm. [13] The route of transmission of the virus from camels to the humans remains to be identified. [6] Camels milk also may also be a source of MERS-CoV. In a study conducted by Doremalen et al found out that 41.7% of the 12 tested camel milk samples were positive for MERS-CoV and it is known that the residents of the Arabian Peninsula commonly drink unpasteurised milk as pasteurization of milk completely inactivates MERS-CoV. [8,15] As all cases did not have contact with camels, there could be another source. [6] As a 32 year old Qatari patient not only gave the history of contact with sick camels, but also had contacted sick goats and sheeps. [8] Small genomic fragments of MERS-CoV was isolated from Taphozous Perforatus bat captured in the vicinity of the residence of human case of MERS in Saudi Arabia also

suggesting insectivorous bats as the source. [10,13] Phylogenetically closely related, viruses have been found in the insectivorous bats in Africa and Europe. [10] Also recent experimental studies have shown that MERS-CoV can infect and replicate in cells of various species including humans, swine, monkey and bats. [12,15]

However, infected animals may shed the virus through nasal and eye discharge, faeces and in their milk and urine. Virus may also be found in organs and meat of an infected animal. As the exact mode of transmission is not fully understood, contaminated dairy, animal products and food products can also be the source of infection. [8] In 2003 during the SARS outbreak a cluster of infections was detected in inhabitants of the same building as that of the index case with digestive symptoms, as the virus aerosol originated from the flat of the patient spread by drainage pipes. [16]

CLINICAL SYMPTOMS AND CASE DEFINITION

Corona virus can cause respiratory and enteric infections and therefore the patients can present with varying symptoms such as high grade fever, non productive cough, shortness of breath, headache, myalgia, nausea, vomiting and diarrhoea. [17] Development of Acute renal failures (ARF) is associated with potential influence on the disease severity in a number of MERS cases. ARF has not been observed earlier in other coronavirus infection including SARS. [18] Severe disease is reported in patients with underlying conditions such as diabetes, chronic cardiac disease, chronic renal disease, chronic lung disease and immunocompromised persons including pregnant females and infants. [8,16,18] Atypical presentation is mostly seen in immunocompromised patients and it can be challenging for the clinicians especially as the digestive symptoms are very common in travelers. [16]

According to WHO revised case definition as of 14 July 2014 for a confirmed case, is any person with laboratory conformation of MERS-CoV infection, irrespective of clinical signs and symptoms. A probable case is a person with febrile, acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease and direct link with a confirmed MERS-CoV case or a travel history to Middle East and when the testing for MERS-CoV is inconclusive. [19]

STRUCTURE, DIVERSITY AND PATHOGENESIS OF CORONA VIRUS

Corona virus is enveloped RNA viruses containing largest single stranded positive sence RNA genome, ranging from 25.5 to 32 Kb in length. [2,20,21] MERS-CoV belongs to C- lineage of Genus Betacoronavirus along with other bat coronavirus such as Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. [5,22] Corona virus possess three major structural proteins: a nucleocapsid protein (N), a small integrated membrane glycoprotein (M,E1) and a large spike glycoprotein (S). The S glycoprotein consists of the S1 domain at the N- terminal with cellular tropism and the membrane proximal S2 domain. The S1 domain i.e. the receptor binding domain of the spike glycoprotein is poorly conserved among coronaviruses, as a result, host receptor usage varies between viral genera and species, as the virus can breach cell type, tissue and host species barrier with relative ease. [20,21]

Also the diversity of the corona virus is facilitated by the infidelity of the RNA dependent RNA polymerase, RNA of coronavirus can undergo recombination, and the presence of unusually large genome. [4] These factors have facilitated the emergence of viruses with new traits that allow the

organism to adapt to new host, sometimes causing zoonotic events. [4]

Coronavirus replication occurs in cytoplasm. [21] The spike glycoprotein mediates membrane fusion and dipeptidyl peptidase 4 (DPP4 also called as CD26) function as a cellular receptor for MERS-CoV, unlike angiotensin- converting enzyme 2 (ACE-2) for SARS-CoV. [22] At tissue level, there is increase permeability of the alveolar capillary interface resulting in pulmonary oedema, hypoxia, type II pneumocyte hyperplasia and cellular infiltration, particularly neutrophil influx. There is upregulation of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-8 and IL-6, CXC- chemokine ligand 10(CXCL-10),CC- chemokine ligand 2(CCL-2) and interferon –γ (INF- γ). This is then followed by increased fibroproliferation and hyaline membrane formation. The progress or the resolution of these gross pathological changes depends on the patient's condition, the presence or absence of any underlying co-morbities. [23]

INVESTIGATION AND TREATMENT

The cases presented with atypical pneumonia on radiological examination. [24] Serum examination of the patients showed the presence of neutrophilia and lymphocytopenia. [4] According to WHO interim guidelines recommendation for laboratory testing for MERS-CoV includes collection of samples from lower respiratory tract such as bronchoalveolar lavage, sputum, tracheal aspirate.Nasopharyngeal swab as the upper respiratory tract samples, along with serum sample , urine and faeces sample. Testing of all samples for other respiratory tract pathogens such as Streptococcus pneumonia, Hemophilus influenza type B, Legionella pneumophila,Influenza viruses, Respiratory syncytial virus, adenovirus should be done along with MERSCoV. [6,11 ,24] The first line Screening assay for MERS-CoV is UpE gene RT- PCR assay. The positive screened samples areconfirmed by either ORF 1a, ORF 1b- RT-PCR assay or by using sequencing amplicons RdRpSeq or N seq assays or viral isolation. [2,24 ,25] Inoculation of sputum samples in LLC-MK2 and Verocells resulted in viral cytopathic changes such as syncytium formation, rounding and detachment. [4,6] For the detection of the antibodies to MERS-CoV Immunofluorescence serum neutralization test and protein microarray technique have been developed. [25,26]

Till date no antivirals are approved for the treatment of MERS-CoV infection norany vaccinesis available for prevention. Therefore the first line of management of the MERS-CoV patients is supportive treatment which includes fluid management, antipyretics, analgesics, respiratory support and antibiotics if required for bacterial superinfections. [27] Potential therapies for MERS-CoV infectionmanagement may includeconvalescent plasma, interferon, lopinavir and polyclonal and monoclonal antibodies where in the benefits of the treatment may exceed the risk of the therapy. [28]

Studies are been conducted for the use of interferon, interferon alfa-2a and Rabivirin. [27,29] In an in vitro study conducted by Jaffer et al, they showed that ribavirin and interferon have anti MERS-CoV activity. When the same combination was used on patients on mechanical ventilation, three of the five patients in the study group developed adverse effects like pancreatic enzyme elevation and hemolysis and all the five patients died. Therefore more studies need to be done to see the effect of the drugs in the earlier stages of the disease as all the five patients were in advanced stages of the disease. [29] In another study conducted by Lu Lu et al, they found that the heptad repeat 1 and 2 (HR 1 and HR 2) domains in the S_2 subunit facilitate viral

and cell membrane fusion and HR2 peptides (HR2P) potentially inhibit S protein mediated cell to cell fusion. Therefore, development of analogues of HR2P can be used as specific anti- MERS-CoV drug to treat patients with MERS-CoV infection. [30] Two recombinant adenoviral based vaccines encoding the full length MERS-CoV S protein (Ad5.MERS-S) and the S1 extracellular domain of S protein (Ad5.MERS-S1) targeting the animal reservoir as a measure to prevent the transmission of MERS-CoV to humans is under trial. [31]

CONCLUSION AND RECOMMENDATIONS

More and more individuals are likely to be infected until the mode of transmission is determined and prompt preventive measures are implemented to break transmission from the source to humans. Also it is very likely that the cases will continue to be exported to other countries, through tourists, travelers, guest workers or pilgrims who might acquire infection from an animal or an environmental source such as nosocomial infection. [9] Thorough and systematic epidemiological investigation along with virological and immunological testing for contact tracing of all household, familial, social and occupational contacts permits to assess the extent of the transmission of the infection by a confirmed case to understand the transmission pattern of the virus. [31,32]

Enhancing infection prevention and control awareness is essential among the health care workers as maximum number of cases were nosocomial in origin indicating poor hospital practices. And awareness among the community members regarding the possible sources and modes of transmission is also very essential as many of the confirmed MERS cases gave the history of contact with the animal either sick or healthy.

It is important that all health care workers apply standard precautions consistently with all patients regardless of their diagnosis in all work places all the time. For general public , when visiting a farm or barn should follow general hygiene practices such as regular hand washing before and after touching the animals, avoiding the sick animals, avoiding drinking raw milk or eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled or cooked. And for people with high risk of severe disease due to MERS-CoV should avoid contact with camels, but if they do need to come in contact, then they should follow appropriate preventive measures. [9]

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