



Review Article

MIDDLE EAST RESPIRATORY SYNDROME CoV: AN EVOLVING VIRAL THREAT TO HUMAN HEALTH

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ABSTRACT

The Middle East respiratory syndrome (MERS) is a highly lethal respiratory disease. It is caused by a novel single-stranded, positive-sense RNA beta corona virus (MERS-CoV). Specific drug treatment exists for MERS and infection prevention and control measures are crucial to prevent spread in health-care facilities. The outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003, led to 8,422 cases and 916 deaths worldwide which highlighted the potential for newly emerging zoonotic corona viruses to transmit from person one to another, especially in healthcare settings, and to cause severe human illness. MERS-CoV is a novel virus among the genus Beta corona virus, which was initially identified in Saudi Arabia in September 2012, in two patients with severe pneumonia. Up to 7 May 2013, the cases in France were identified, 30 cases had been confirmed as infected by the corona virus worldwide which included four diagnosed in the United Kingdom (UK) and two in Germany. Two cases of severe respiratory infection have been confirmed as caused by a novel corona virus. The case guideline has been issued by the World Health Organization (WHO) which is mainly based on acute respiratory illness, pneumonia and travel history. The incubation time is crucial as it is playing a major role in suspecting Saudi Arabia and Qatar, and define its clinical features. The presumed length of the incubation period was compared with known incubation periods of human corona virus infections including that of severe acute respiratory syndrome (SARS). Our main aim of the article is to give overview on the MERS CoV disease pointing out its symptoms, diagnosis, spread, therapy and cases reported up to now. This is a uncommon virus and details about MERS is still unknown as it is often confused as some common viral respiratory disease so we have tried to collect the possible data and reports in our content.

KEY WORDS: Human Corona Virus, MERS- Middle East Respiratory Syndrome, Serum, Pneumonia, SARS (Serum Acute Respiratory Syndrome)

INTRODUCTION

First case of Middle East respiratory disease is reported in hospital in Jeddah, Saudi Arabia, 2012.

There many people were killed by the unrecognized corona virus (MERS COV) isolated from the patient which was similar to severe acute respiratory syndrome corona virus (SARS). This virus was designated by human corona virus EMC, but after some time it was rename MERS COV with global consensus¹

The genome structure of MERS CoV is dipeptidyl peptides 4(DPP, also known as CD26) which is similar to the host cell receptor for the cell entry. By the reverse genetics of virus genome we can quickly develop a molecular diagnostic test. This virus is most prone to the patient which are suffering from the disease like diabetes, renal diseases, it may also due to the respiratory droplet transmission.²

Corona viruses (CoV) are large positive-stranded RNA viruses causing mainly respiratory and enteric disease in a range of animals and in humans. Humans are known to maintain circulation of four different human corona viruses (hCoV) at a global population level. These are part of the spectrum of agents that cause the common cold. The SARS-CoV constitutes a fifth CoV, which was in circulation for a limited time during 2002 and 2003, when a novel virus appeared in humans and caused an outbreak affecting at least 8,000 people. Mortality was high, at ca. 10%. Symptoms matched the clinical picture of acute primary viral pneumonia, termed Severe Acute Respiratory Syndrome (SARS).

Spread of virus

It has a covering of RNA virus which have a crown like projection seen under electron microscopy. This virus are divided into three genera; alpha, beta, gamma corona virus. The main host of this virus are animals such as camels and bats which are responsible for causing wide variety of important diseases. Human corona virus are generally from the alpha and beta genera. The first case was reported in 1996 in which human corona virus repeatedly noticed which frequent causes of common cold, exacerbation of asthma and it also contribute lower respiratory tract infections in children as well as in elder, in some cases diarrhea. Human COV are found all around the world but it is more active in winter and early months of spring climates⁴ Infected birds and mammals are from the family of corona virus. The mode of transmission of MERS COV to human not know yet².

Structure of Virus

Corona virus is a single stranded positive sense RNA viruses with size 28-32 kb which enters in the host cells and bind with the receptor, dipeptidyl peptides 4. Protease cleavage of S protein is required for the fusion of the virus to release of genomic RNA into the cytoplasm. The transcription and replication of viral RNA occurs on the double membrane vesicles and other membranous structures, which is derived from the endoplasmic reticulum. This transcription for the seven sub genomic m RNA s which occur through the negative strand sub genomic RNA intermediates. Sub genomic RNAs 3 are joined with 5 end of the genome¹

Strains of Virus

Three strains of MERS corona virus were isolated from dromedary camels in Saudi Arabia (Dromedary/Al-Hasa-KFU-HKU13/2013[AH13] and Dromedary/ Al-Hasa-KFUHKU19D/2013 [AH19D]) and Egypt (Dromedary/Egypt-NRCE-HKU270/2013[NRCE-HKU270]). When the replication kinetics of these three dromedary strains were analysed and compared with the prototype human MERS-CoV strain EMC2012 (hMERS-CoV EMC 2012) in both cell culture (VERO E6 cells) as well as in ex-vivo human respiratory tract tissues. In cell culture, all four strains showed similar levels of replication. Whereas all the four strains were able to infect the ex-vivo human bronchial and lung tissues thus showing competency for human.

The research conducted by Chan et al (2014) concludes that dromedary MERS-CoV strains from both the Gulf States and genetically diverse viruses from Egypt can cause a serious risk of infection in humans. Hence, unexplained viral pneumonias in Africa, as well as across the Middle East, should be investigated for MERS-CoV involvement³.

Symptoms

MERS can cause an acute highly lethal pneumonia in its severe form. Its consequences include renal dysfunction or direct infection of the kidney. Infection of the kidney is due to high levels of DPP4. To understand the sites of infection, patient tissue samples are analysed. The understanding of pathogenesis came from the experimental studies of infected animals.

Animals like macaques, marmosets and camels can be infected experimentally MERS-CoV. On radiological examination, it was found that macaques had developed mild clinical disease with the symptoms of inflammatory cell infiltration. According to the electron micrograph of MERS- COV is a large single membrane vesicles of the peripheral cell. Virus spikes are visible through a electron microscopy in which the RNA genome is encapsulated in the N protein. This information was provided by the Montserrat Barcena, Ronald Limpens and Eric Snijder (Leiden University Medical Center, Netherlands)⁴.

MERS- COV is showing a viral RNA structure of proteins spike (S), with envelope (E), matrix (M), and nucleocapsulated (N). MERS virus is infected the human airways cells and it assessed for the viral antigen by indirect immune fluorescence assay with an antibody of MERS- COV N antibody. The green color of MERS COV cell indicated positive MERS COV by staining with blue stain. Serology of MERS can also done by this assay. This assay is explain by the Christine Wohlford – Lenane (University of Iowa , Iowa city, IA)⁵.

Transmission from camels to human beings

Transmission of MERS-CoV infection to human has been linked from camels, although some of the patients also have a history of exposure from camels. It was interpreted that the patients who consume unpasteurized camel milk might be exposed to the infectious virus. The viruses were isolated from infected camels and patients. The interpretation of these studies becomes complicated due to the fact that the RNA viruses present in the infected hosts, also including MERS-CoV infected camels, consist of swarms of related RNA molecules. While transmission to a new host, some of the members of RNA virus swarm gets transmitted, due to which the isolation of exact same virus from recipients and donors becomes difficult. The infection occurs at a younger age in the camels with frequent boosting. This is suggested by the fact that the adult camels which are anti-MERS-CoV seropositive are very high in proportion. In most of the cases, lack of human contact with the camels raises the question

or a possibility that the transmission is person to person primarily, or from some other intermediate host.

A conclusion was made that some of the infections of the camels may be a result of person to camel transmission. Some of the additional intermediate hosts like a corona virus, isolated from European Hedgehogs, very similar to MERS-CoV, might be involved. All the combined results suggest that the confirmed source of human infection is transmission from camels only because many details regarding camel to person transmission still remains unclear. Although the disease is seasonal, still the cases of MERS are reported throughout the year. The first cases were reported in April & June, 2012, and then a gradual increase in the cases was reported as years passed. The increase in the number of infections reflects that it is due to the newly infected young camels¹.

Infection Control and Preventive Measures

The only available means to limit or control the spread of MERS infection are public health measures because currently, there are no drug therapies or natural immunity and vaccines that are effective and available against MERS-CoV infection. The measures to be taken are firstly, identification of the infected persons and then implementing full precautions and control methods regarding the transmission of the disease. In addition to this, further surveillance is also essential for the cases of acute or severe respiratory disease, by diagnostic testing, strict adherence to control precautions and also for the careful monitoring of close contacts. The close contacts may be the persons who provide care to the ill ones or the persons having physical contact with the ill ones. The advice from WHO for home care management of patients is mainly targeted towards public health measures only for the control of the infection⁴

This virus is first time are recognized in 1960s, which causes mild respiratory tract infection in human⁶. This virus first time was isolated from a patient who is suffering from the respiratory disorder in June, 2012 in Jeddah, Saudi Arabia. In May 31, 2015, 1180 laboratory confirmed cases around 483 deaths have been reported to WHO.⁷

According to the recent discovery by the public health experts and healthcare a new human corona virus is discovered which causes serious respiratory disorder. On 20 and 23 September two cases are found with the connection to Saudi Arabia which were communicated through ProMED respectively⁸. Corona virus is RNA infected virus which affected a large number of animals including domestic as well as companion animals and bats⁹. By the outbreak of 2003 around 8,000 people across three continents with lethal ratio 10% from the severe acute respiratory syndrome (SARS)¹⁰

According ProMED report a novel human corona virus is recovered on 20 September in Saudi Arabia an adult male die in 2012 by suffering from a acute respiratory disorder, such as pneumonia and renal failure² The Health Protection Agency(HPA) on 8 February 2013 of London, United Kingdom(UK), were confirmed that this infection of novel corona virus (nCoV) are present in patient an intensive care unit, this virus symptoms were found in a patient with in 10 who is travelled both Pakistan and Saudi Arabia¹¹

On 7 May 2013 in France around 30 cases were confirmed as infected by this virus worldwide in which four were diagnose in United Kingdom (UK) and two were in Germany^{12,13}. On 13 June 2012 a 60 year old patient is suffering from pneumonia in Jeddah in Saudi Arabia with a seven day history of respiratory symptoms. The patient is died due to the renal failure on 24 June 2012. A beta corona virus was isolated in Saudi Arabia and DNA sequence study at the Erasmus Medical Centre (EMC) in Rotterdam, Netherlands¹⁴.

A preschool child were admitted to a Hong Kong hospital from Saudi Arabia who was kept an isolated ward in early October 2012, which were infected by a corona virus. A symptom of fever, cough and vomiting, but not a symptom of pneumonia. One person had a fever two day earlier, but before admission he recover¹⁵.

The novel human beta corona virus (hCoV-EMC) first time found in Middle East in 2012¹⁶.

In Arabian Peninsula, 12 cases were confirmed by WHO on 18 Feb 2013¹⁷. 50 laboratory confirmed cases of the disease had occurred worldwide till 30 May 2013¹⁸. The first assays for the diagnoses of novel corona virus was described by Corman et al in Sep 2012¹⁹. A case of NCoV infection was informed by the International Health Regulations to Robert Koch Institute in Berlin, Germany on 22 Nov 2012. The case which was reported of a patient in Quatari, who was in his forties was treated in Germany²⁰.

Diagnosis

CoV virus when checked with Real Time Polymerase Chain Reaction (RT-PCR) showed two or three RNA targets or alternatively by sequencing²¹. When these methods of RTPCR provide negative results then we can use serological datas to detect the specific antibodies in patients and people in constant contact with them. Collecting the serological data from various regions may be problematic beacuse the disease is widespread so to draw some interpretation from serology is time taking²².

Treatment

The main methods for treatment of MERS are helpful. According to the current data one interpretation is drawn which includes patient sera, interferon and lopinavir for a specific therapy. There is no cure from any other therapy other than antiviral drugs. Some Monoclonal and polyclonal antibodies are in developing phase for the treatment²³.

Infection control and preventive measures

As there is no specific therapy to treat MERS affected patients and no vaccine or antibody against MERS infection so the only method to control its spread is to take public health measures. These involve to target the patient and completely prevent spread of any infection from them to healthy ones. The suspected individual with the disease in isolated, diagnosed, monitored and samples are collected from them. Now careful examination is done for people in close physical contact or those visiting the patient. WHO advices to take healthy home care management of patients with MERS-CoV virus infection^{24,25,26}.

CONCLUSION

This disease conditions are evolving and there are many unknown cases to consider this hypothesis generation and control measures. There is strong evidence that a new virus is causing a severe disease in patients. On basis of assumptions it can be concluded that the virus poses threat to people's health. There may have been many other cases in the past that were not identified but with the serological testing of stored sera and other specimens from such cases will be important in finding out the root cause. Most of the cases of MERS are found being in Middle East region. Out of the cases majority people have been in contact with camels which might have shed the virus.^{27,29}

Serological testing will also determine the origin, multiplication and transfer of the virus from various animals to the human species. It will also clearly define the symptoms and the physiology of the new virus. The findings of these cases occurring in Europe and EEA/EU countries suggest that the virus database is still less due to fewer sample collections across the borders. So a suggestive conclusion to the virologists and public health agencies is drawn to collect more

samples and clearly define the serological assays for the virus. Our results will help in the awareness and the spread of the human corona virus which is still not commonly distinguished by the health practitioners and is confused as a ordinary pneumonia disease²⁸.

Our assessment, is based on the limited database currently available, is that the risk of wide spread transmission which is resulting in this severe disease is low. However, the emergence of CoV (coronavirus) requires a thorough assessment which is now being coordinated by international health agencies²⁷.

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