Human pathogenic Corona viruses (HCoVs) and their types and newly emerged COVID-19

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Abstract

The first corona virus which is isolated in 1930s from domestic fowls was Infectious bronchitis virus (IBV). These corona viruses infect mammals in the upper respiratory tract and sometimes are responsible for causing viral infections in humans. Although the different types of corona viruses have similar mode of infection but they lead to different health issues. Mostly are not harmful to human but some like recently emerged COVID-19 sets up an alarming situation. In this review article we will discuss about different types of human pathogenic corona viruses with a special reference to COVID-19.

Introduction

Coronaviruses contain positive sense single stranded RNA as a genetic material. The enveloped Corona viruses belong to the subfamily of Orthocoronavirinae which lies in family coronoviridae. They have been classified under Nidovirales order. There are three subfamily of Corona viruses coronavirus α, coronavirus β, coronavirus γ, and coronavirus delta. Several pathogens of animal and human origin are present within the family of coronavirus (Weiss et al., 2005; Banerjee et al., 2019).

Nidovirales are united in the order of monophyletic group of animal RNA viruses. This order possess the RNA genome that ranges from 26kb to 32kb that consist of corona viruses that are distantly related such as Toro viruses and Ron viruses (Gorbalenya et al., 2006). The murine coronavirus prototype strain JHM was isolated in 1949 (Cheever et al., 1949; Bailey, et al., 1949). Several studies have been conducted since 1970s on replicative pattern and molecular mechanisms of replication of several coronaviruses. For the research carried out in the field of veterinary there are various types of animal corona viruses such as BCoV: bovine coronavirus, TGEV: porcine transmissible gastroenteritis virus, and IBV: avian infectious bronchitis viruses. The murine coronavirus model is used to study human diseases.

More than 50 years Coronaviruses have been described and was believed it may infect animals as well as humans so was less studied, but in 2002 The outbreak of on epidemic in 2012 that was named as SARS causing severe acute respiratory complications with mortality of 10% and another epidemic Middle East respiratory syndrome (MERS) suggested that coronaviruses can be deadly and were actually capable of crossing the species barrier and infecting humans (Schoeman & Fielding 2019). The MERS- CoV as well
as SARS- CoV, both were found to belong to the family of β- coronavirus (Zumla et al., 2015). Recently, a novel coronavirus, very similar the MERS and SARS coronaviruses, spread in China around late December in 2019 and is named COVID- 19 (Cohen & Normile 2020 ; Zhu, et al., 2020). and the reports suggest that transmission is through close contacts between humans, some reported that it could travel from one species to other however the fact still remains unclear. The newly emerged corona virus COVID- 19 has same genome of single stranded RNA which is positive- sense. The sequence of covid-19 was studied and the reported that genome anatomy this novel coronavirus is same as SARS and MERS thus it also belongs to β- coronaviruses (Chen et al 2020). After analysis of genome the COVID- 19 was 82% or more identical to SARS (Zhang et al., 2020; Chan et al., 2020) Currently COVID- 19 has spread as a worldwide pandemic with no vaccine available till date.

Diversity of CoV pathogenesis

Depending the type, CoVs have various tissue tropism as well as various host range. According to earlier studies present, the corona viruses from family α- coronavirus and β- coronavirus only infected mammals, while as γ- coronavirus, and delta- coronavirus infection is limited to avian and fish but were later found to infect mammals too (Woo et al., 2012; Cui et al., 2019) Before the emergence of COVID-19, researcher were aware of only six CoVs that could transmit to human and were capable of causing serious to mild illness and respiratory diseases.

Human corona viruses such as HCoV- NL63, HKU1, HCoV- 229E, HCoV- OC43, SARS-CoVs and MERS-CoVs, out of which the former four were found to cause upper respiratory disease with mild complications, and latter two CoVs were found to cause a severe respiratory-syndrome in humans by infecting lower part of respiratory tract in human (Su et al., 2016; Fehr et al 2015). The new HCoV, COVID-19, from β- coronavirus family, can cause pneumonia in humans also infects the lower respiratory tract, but as compared to SARS and MERS, it seems that the symptoms of COVID-19 are milder.

The major human pathogenic CoVs

HCoV-229E

HCoV-229E is human corona virus which causes common cold, having RNA positive-stranded virus in the group 1 (Holmes et al., 2001). A cell surface metalloprotease (Human aminopeptidase N (hAPN), found on macrophages, synaptic junctions, on apical membranes of intestinal cells, also present on epithelial cells of lung and kidney, act as receptor for HCoV-229E (Yeager, et al 1992). The spike glycoprotein represented as S protein is 200kDa. This S protein contains 15 amino acid while the S1 domain at N terminal contains 16-560 amino acids, S2 domain consists of 561-1173 amino acids and also having repeats of heptad regions, the area of transmembrane domain contains almost 1117 to 1138 amino acid residues, and a short cytoplasmic tail which consist of 1139 to 1173 amino acids and a cluster of carboxy-terminal cysteine (Raabe et al., 1990). For N-glycosylation S protein that is spike protein is
having 30 possible sites. It is possible that the spikes seem to be closely related to coronavirus of pigs, both having S glycoprotein trimers (Delmas et al., 1990).

HCoV-229E infects humans, so pathogenesis studies are carried out on only human subjects (Tyrrell et al., 1979). Currently two isolates of HCoV-229E were separated from cell cultures of human origin, including the Hamre and Procknow isolated strain identified in 1966 in United States (Hamre et al., 1966) and the isolate of LP strain by researcher in united kingdoms in 1968 (Tyrrell et al., 1968).

**HCoV-NL63**

HCoV-NL63 was reported in newborns and adults with impaired immune system with respiratory tract illness (Hofmann et al., 2005; Allander et al., 2005). It is a group-I CoV with close relation to HCoV-229E (Hofmann et al., 2005) HCoV-229E has CD13 as a receptor for targeting of host cells. Because spike protein of corona virus NL63 and corona virus 229E-S proteins are at least 56% of identical amino acid so based on this fact corona virus NL63 also has CD13 receptor for facilitating entry inside host cell. The N terminus of spike protein of HCoV-NL63-S has 179 amino acid sequence which has homology with other corona virus spike proteins which can probably change the specificity of NL63-S receptor as compared to 229E-S (Hofmann et al., 2005).

Human Corona virus OC43 and 229E are groups I and II member, respectively, and is 30% responsible for observed cases of common cold (Gierer et al., 2013). While as Corona viruses such SARS causes a critical condition of respiratory tract illness (RTI) with fatal more than 10% of infected individuals (Yang et al., 2005). The pathogenicity and factors leading to the infectivity of Corona viruses are not fully understood but a role for the spike protein has a role in pathogenesis in facilitating the entry and infect the target host as well as helps in viral replication inside the host cell (Sui, et al., 2004).

**HCoV-HKU1**

HKU1 is a novel human pathogen belongs to the group II virus from was reported in Hong Kong in patient having chronic pulmonary disease, mostly in adult described in 2005 (Woo et al., 2005). At first the HKU1 case was reported in elderly patients with major respiratory and cardiovascular complications. Patients with HKU1 infections had mortality that 2 patients aged 66 and 74 would die out of 10 patients, with both having another underlying serious diseases died (Woo et al., 2005). The HCoV-HKU1 associated symptoms generally include coughing, fever, rhinorrhea, and also severe symptoms like pneumonia and bronchiolitis (Sloots et al., 2006; Lau et al., 2006). The HCoV-HKU1 infection might also be involved in causing gastrointestinal complications (Vabret et al., 2006).

The genome of HCoV-HKU1 is 29,926-nucleotide, polyadenylated RNA (Woo et al., 2005). It has lowest GC content i.e. 32% among all known coronaviruses. It belongs to group 2 and genetic makeup is the alike as that of other members of group II. The protein genes responsible for attachment are present at N gene position (ORF8) and between the S and E genes (ORF4). The transcription regulatory sequence (TRS)
which is common is probably positioned within the AAUCUAAAC sequence. At position 29708-29760 nucleotide downstream, there is a presence of pseudoknot structure. In group II coronaviruses both RNA structures are conserved and are important for virus replication (Goebel et al., 2004 Williams et al., 1999).

**HCoV-OC43**

HCoV-OC43 was first obtained from the volunteers in 1967 in Common Cold Unit, Salisbury, United Kingdom. It was found responsible for 5%-30% of all common colds during winters and spring season (Larson et al. 1980). Its incubation period is usually 2 to 4 days prior to infection. The symptoms include Mild respiratory tract infections. The initial cultures of it were established on nasal organ cultures and ciliated human embryonic tracheal cultures (McIntosh et al., 1967). It is believed to be the most commonly encountered by human but limited knowledge is available about its evolution with in humans and no similar molecular epidemiology studies have been performed (Lau et al., 2011).

The HCoV-OC43 complete genome sequences laboratory strain can be obtained from the ATCC: American Type Culture Collection and another a clinical isolate that was obtained from Paris. Researchers analysed both genomes and found out that each genome was 30,713 nucleotides long excluding the poly A (Adinine) tail, and vary by six nucleotides only. The 6 nucleotides give rise to only two amino acid substitutions, I958F spike protein gene and a nucleocapsid protein gene V81A and these six mutations were randomly distributed all over the genome (St-Jean et al., 2004).

The HCoV-OC43 is group ii member alike SARS (Snijder et al., 2003). In contrast with the nucleotide sequences and amino acids of SARS (Marra et al., 2003) the HCoV-OC43 share wide range of homology with SARS at some of the motifs that are involved in its replication and pathogenesis. One of the important motif HCoV-OC43 that is pf 3CL pro motif also share important level of identity with the one of SARS-HCoV (Thiel et al., 2003).

**SARS-CoV**

Severe acute respiratory syndrome: SARS, is highly contagious atypical pneumonia having high mortality rate (Fouchier et al., 2004; Simmons et al., 2004). The infection with severe acute SARS-CoV is responsible for causing a severe respiratory tract illness having a fatality in more than 10% of infected individuals. The incubation period of this viral infection is 2 to 7 days. Symptoms is fever followed by a dry cough after few days and difficulty in breathing. In February 2003, SARS outbreak was reported from Guangdong Province, China by World Health Organization (WHO) (World Health Organization, 2003). But the emergence of “an atypical pneumonia” first cases were reported in late 2002 in Guangdong Province, China (Parry, J 2003). By the end of April 2003, there were reports of over 4300 SARS cases and over 250 deaths by SARS were reported from more than 25 countries in the world by WHO.
A novel SARS-CoV was isolated from lungs and sputa of patients and cultivated on cell line of monkey kidney origin (Ksiazek et al., 2003; Peiris et al., 2003). The sequence information of CoV-SARS confirmed that this was a previously unrecognized CoV (Rota et al., 2003; Snijder et al., 2003). The genome of SARS-CoV is a 29,727-nucleotide, polyadenylated RNA, with 41% of GC content. SARS-CoV replication gene consists of about 2/3 of its genome, encoding two polyproteins from ORF1a and ORF1b. These two polyproteins undergo co-translational type of proteolytic processing. The downstream of rep consists of four ORFs (open reading frames) encoding structural proteins. The SARS-CoV genome has 11 ORFs and the organization of its genome is similar to other coronaviruses (Rota et al., 2003).

The binding in corona virus, to receptor host cells followed by membrane fusion is, facilitated by large type-I membrane glycoproteins called spike proteins (Sánchez et al., 1999). In case of SARS corona virus, its spike protein has potential 23 N-linked glycosylation sites. The motifs in S protien present at amino and carboxyl termini in Corona viruses, which are also present SARS spike protein, but in SARS the S1 domain is less conserved than S2 domain. The S protein of SARS-CoV contains a amino acid signal sequence which is hydrophobic in nature. The transmembrane domain is present at C terminus having cysteine residues rich tail which is highly conserved among SARS-CoV (Rota et al., 2003).

**MERS-CoV**

Another human coronavirus causes Middle East respiratory syndrome and called MERS coronavirus. Earlier it was called HCoV EMC: “novel human coronavirus Erasmus Medical Center”. In year 2012, Zaki et al make first reports of MERS from Saudi Arabia (Butler, D 2012). There were at least 2279 cases of MERS reported by World Health Organization, in 27 countries since 2012 out of which 806 deaths were reported from MERS on Feb. 13, 2019 which is 30% of total patients with MERS. In Saudi Arabia an approximate of 80% of MERS cases have been reported (World Health Organization., 2019).

MERS-CoV is the β coronaviruses belongs to lineage-C (Chan et al., 2015; Zaki et al., 2012). Even though bats are carriers for most of coronaviruses, MERS corona virus was reported from dromedary camels which has been found the only carrier so far. Furthermore, MERS corona virus that was isolated from dromedary camels was found to be closely related corona virus in bat species (Eckerle et al., 2014; Assiri et al., 2016). WHO reports suggested that transmits of MERS is human to human and occurs in Middle East countries (World Health Organization., 2019).

In MERS-CoV, like other CoVs, S protein is responsible for entry, by attaching itself to host cell. MERS corona virus host cell receptors are known as dipeptidyl peptidase-4 (Xia et al., 2014; Lu et al., 2013). Upon attachment of MERS spike proteins with its host receptor DPP4 receptor the virus gets host cell access and triggers signals which induces the suppression of immune system of patients infected, therefore enabling virus to replicate and spread (Al-Qahtani et al., 2017).
COVID-19

A COVID-19 novel coronavirus outbreak was reported in China, Wuhan district in late December year 2019 which was earlier known as 2019-nCoV (Wu et al., 2020; Huang, et al., 2019) which has been declared as pandemic by WHO, subsequently affected more than 26 countries worldwide. As per the report issued on 06 April 2020 by WHO and worldmetrometers.info the total global number of COVID-19 cases has surpassed 1,278,528 (World Health Organization 2020; https://www.worldometers.info/coronavirus/). The deaths due to COVID-19 worldwide is 69,757 and recovered cases worldwide are 266,732. Over all, COVID-19 is an acute determined disease but it can also be fatal, with a 2% case fatality rate.

Researcher has reported that COVID-19 is related and much alike to SARS caused by coronavirus and MERS. It can also cause pneumonia and acute respiratory distress syndrome (Huang, et al., 2019; Graham et al., 2013).

Till date, patients with COVID-19 has mild symptoms like dry cough, sore throat, fever in some cases diarrhoea and vomiting. Most of patients with covid-19 have naturally resolved. However, some patients with age group 56 years and older have fatal complications like multiple organ failure, severe pneumonia, and ARDS (Chen et al., 2020). Patients of COVID-19 in need of intensive care support (ICU) are elderly people and had multiple underlying complication like immuno compromised, cardiovascular, cerebrovascular, endocrine, digestive, and respiratory disease. (Wang et al., 2020).

According to a study by Chen et al 2020, the sequence of CoVID-19 is comparatively different from other six coronavirus The sequence of covid-19 was studied and the reported that genome anatomy this novel coronavirus is same as SARS and MERS thus it also belongs to β- coronaviruses (Chen et al 2020). After analysis of genome the COVID-19 was 82% or more identical to SARS (Zhang et al., 2020; Chan et al., 2020). As per reports SARS can directly transfer to human from civet cat as it was the carrier of SARS and MER can be directly transmitted to humans from dromedary camels, and the reservoir of these viruses was in species of bats, but the source of origin of COVID-19 needs to be investigated further (Tao et al., 2016; Cui et al., 2019; Zhou, et al., 2018). The genome of COVID-19 genome is a single-stranded RNA which is positive-sense and is enveloped virus. The genome measure 50–200 nm in diameter. The crown-like appearance is given by its spikes that made up of glycoprotein s (Chen et al 2020). Transmission rates are unknown for COVID-19.

One recent study suggests that the COVID-19 is not a mosaic and could related with the Bat CoV RaTG13 detected in bats of china in Yunnan Province (Zhou et al., 2020). The genetic analysis and after reported by various ongoing research on newly emerged COVID-19 it is seen that similarity between the COVID-19 and RaTG13 suggest that the latter does not deliver the same variant responsible for the outbreak in humans, but the theory that COVID-19 has originated from bats can be true to some extent.

Table.1 List of important human pathogenic coronaviruses (Chen et al., 2020).
<table>
<thead>
<tr>
<th>VIRUS</th>
<th>GENUS</th>
<th>HOST</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human CoV-229E (Chen et al., 2020)</td>
<td>Alpha</td>
<td>Human</td>
<td>Respiratory Infections, mild</td>
</tr>
<tr>
<td>Human CoV-NL63 (Chen et al., 2020)</td>
<td>Alpha</td>
<td>Human</td>
<td>Respiratory Infections, mild</td>
</tr>
<tr>
<td>Human CoV-HKU1 (Chen et al., 2020)</td>
<td>Beta</td>
<td>Human</td>
<td>Pneumonia, critical</td>
</tr>
<tr>
<td>Human CoV-OC43 (Chen et al., 2020)</td>
<td>Beta</td>
<td>Human</td>
<td>Respiratory Infections, mild</td>
</tr>
<tr>
<td>SARS-CoV (Chen et al., 2020)</td>
<td>Beta</td>
<td>Human</td>
<td>Upper respiratory infection, critical with 10% mortality</td>
</tr>
<tr>
<td>MERS-CoV (Chen et al., 2020)</td>
<td>Beta</td>
<td>Human</td>
<td>Upper respiratory infection, critical with 37% mortality</td>
</tr>
<tr>
<td>COVID-19 (Chen et al., 2020)</td>
<td>Beta</td>
<td>Human</td>
<td>Pneumonia with lower respiratory tract infection, criticals depending on underlying disease and age group 2-4% mortality</td>
</tr>
</tbody>
</table>

**Conclusion**

In Current scenario the outbreak COVID-19 has been declared as Health emergency worldwide. The number of cases COVID-19 is continuously going up day by day. The total global number of COVID-19 cases has surpassed 1,278,528 and the deaths due to COVID-19 worldwide is 69,757. Currently there is no vaccine available and the main treatment for tackling this pandemic is supportive. Although quarantine alone won’t suffice to prevent the spread of COVID-19, and the influence of this viral infection is one of increasing concern all over the globe.

After the outbreak of epidemics SARS and MERS, significant research came into existence to develop a new antiviral agents and vaccines that can target CoVs proteases, polymerases, MTases, as well as the proteins that facilitated entry inside host, but none passed the clinical trials. However blood of recovering patient and obtaining Plasma and antibodies from it can be used in treatment of COVID-19. Currently COVID-19 has spread as a worldwide pandemic with no vaccine available till date.

**References**


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