ANNQUEST JULY 2020
ISSN:2321-3043
www.stannsannquest.com

OUTBREAK OF CORONA VIRUS-19 : A REVIEW OF LIFECYCLE, CLINICAL FINDINGS AND TREATMENT METHODS

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History

Viral diseases has been continuously emerging and causing a serious public health concern globally. These viral epidemics like SARS-CoV in 2002, H1N1 in 2009, the recent one MERS- CoV in 2012 and the current one Covid19 have a devastating effect on human life.A brief outline of the current pandemic, that started with unexplained low respiratory infections detected in Wuhan, one of the largest metropolitan area in China's Hubei province was first reported to WHO on December 31, 2019. Though the infection by the virus was already existing but it took time to be identified as a viral infection. The earlier cases were classified as suffering from pneumonia with a n unknown cause. However, the Chinese Center for Disease Control conducted an intensive investigation to unravel the aetiology of the illness, which was later attributed to the infections caused by the novel Coronavirus family. There is a strong correlation of seasonal incidence in the outbreak of such infectious diseases(1).

Introduction

The name "coronavirus" is derived from Latin *corona*, meaning "crown" or "wreath", itself a borrowing from Greek, garland, wreath. The name was coined byJune Almeida and David Tyrrell who first observed and studied human coronaviruses. The word was first used in print in 1968 by an informal group of virologists in the journal Nature to designate the new family of viruses.The name refers to the characteristic appearance ofvirions(the infective form of the virus) by electron microscopy, which have a fringe of large, bulbous surface projections creating an image reminiscent of the solar corona or halo. This morphology is created by the viral spikes, which are proteins on the surface of the virus.

Corona viruses are a group of viruses(RNA viruses), which causes diseases in mammals, birds and animals. In humans, these viruses cause respiratory tract infections that can range from mild to lethal. Mild illnesses include some cases of the common cold (which is caused also by certain other viruses, predominantly rhinoviruses), while more lethal varieties can cause SARS, MERS, and COVID-19. Coronaviruses cause acute, mild upper respiratory infection (common cold). Symptoms in other species vary: in chickens, they cause an upper respiratory tract disease, while in cows and pigs they cause diarrhea.

Structure

These virues are spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein projections. They are enveloped viruses with a positive sensesingle stranded RNA genomeand anucleocapsid of helical symmetry. This is wrapped in a icosahedral protein shell. Thegenome size of coronaviruses ranges from approximately 26 to 32 kilobases, one of the largest among RNA viruses. They

have characteristic club-shaped spikes that project from their surface, which in electron micrograph create an image reminiscent of thesolar corona, from which their name derives.

Genome

Spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid made of matrix protein. The envelope has club-shaped glycoprotein projections. They are enveloped viruses with a positive-sense single-strandedRNAgenome and a nucleocapsid.This is wrapped in a icosahedral protein shell. The genome sizeof coronaviruses ranges from nearly 26 to 32 kilobases, which is one of the largest among RNA viruses.

Life cycle

Infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell receptor. After attachment, a host cell protease cleaves and activates the receptor-attached spike protein. Later, cleavage and activation allows thevirus to enterthe host cell by endocytosis or through fusion of the viral envelop with the host membrane.

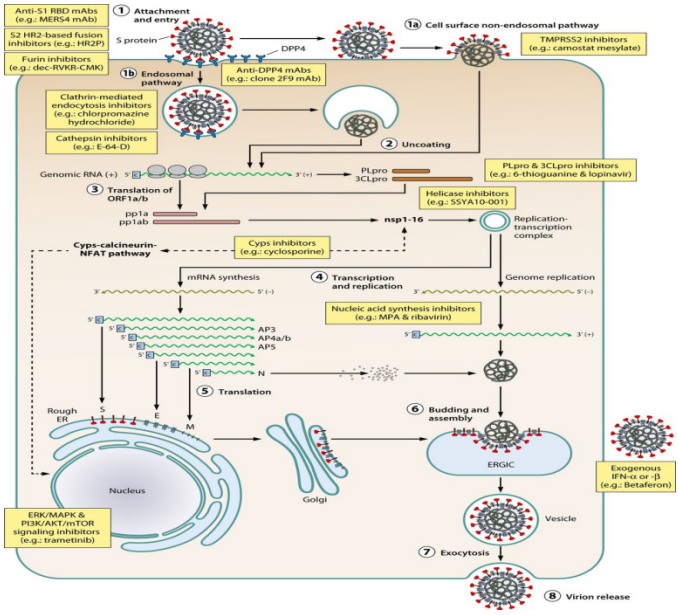
Upon entry into the host cell, the virus particle is uncoated, and itsgenome enters thecell cytoplasm. The coronavirus RNA genome has a5' methylated cap and a 3' polyadenylated tail, which allows the RNA to attach to the host cell ribosome for translation. The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a longpolypeptide. This polypeptide with its own proteolytic activity,cleaves the polypeptide into multiple nonstructural proteins(1).

Replication

A number of the nonstructural proteins coalesce to form a multi-protein Replicase-Transcriptase Complex(RTC). The main replicase-transcriptase protein is the RNA-dependent RNA polymerase(Reverse Transcriptase). It is involved in the replication and transcription of Single stranded RNA molecule. The other nonstructural proteins in the complex assist in the replication and transcription process. The exoribonuclease nonstructural protein, provides extra benefits to replication by providing a proofreading function which the RNA-dependent RNA polymerase lacks.

One of the main functions of the complex is to replicate the viral genome. Reverse Transcriptase directly mediates the synthesis of negative-sense genomic RNA from the positive-sense genomic RNA. This is followed by the replication of positive-sense genomic RNA from the negative-sense genomic RNA.The other important function of the complex is to transcribe the viral genome. Reverse Transcriptase directly mediates the synthesis of negative-sense subgenomic RNA molecules from the positive-sense genomic RNA, which is later followed by the transcription of these negative-sense subgenomic RNA molecules to their corresponding positive-sense mRNAs.

The replicated positive-sense genomic RNA is the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host ribosomes into the structural proteins and a number of other proteins. RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins glycoprotein(S), envelope(E), and membrane(M) move along the secretory pathway into the Golgi complex. There, the membrane proteins direct most protein-protein interactions required for assembly of the virus following



its binding to the nucleocapsid. Progeny viruses are then released from the host cell by exocytosis through secretory vesicles(6).

Clinical findings

Covid-19 primarily spreads majorly through direct contact by an infected person, droplets and respiratory secretions. However, clinical findings at Guangdong(China) studies showed the presence of virus in the fecal swabs and blood, indicating the multiple paths of transmission.The incubation period is 2-14 days. The elderly people with a previous history of diseases are more susceptible, especially the age group of 47-59 yrs. The symptoms show fever, malaise and cough. Most of the patients present mild flu-like symptoms and few of them who are critical present with acute respiratory distress, respiratory failure and multiple organ failure followed by death. The other symptoms reported by Prof. Nan-Shan zhong and his team on 1099 samples showed that patients had fever(88.7%), cough(67.8%), fatigue(38.1%), sputum production(33.4%), shortness of breath(18.6%), sore throat(13.9%), and headache(13.6%). Apart from this some of the patients also manifested gastrointestinal symptoms, with diarrhea(3.8%) and vomiting(5.0%).

Fever and cough were the dominant symptoms whereas upper respiratory symptoms and gastrointestinal symptoms were rare indicating the differences in viral tropism which was not found with SARS-CoV, MERS-CoV, and influenza. The elderly and those with disorders (i.e, hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular disease), developed rapidly into acute respiratory distress syndrome, septic shock, metabolic acidosis hard to correct and coagulation dysfunction, even leading to death.

Most children hospitalized in New York reported no symptoms. But some of these children had respiratory symptoms with high fever, gastro-intestinal inflammation, presented with nausea, vomi ting, stomach upset and skin infections characteristically covid toes. The clinicians reported that these children are not postitve for the virus but positive against the antibodies of the virus. This could be due to the delayed response of people recovering from infection. The antibodies so produced are eliciting an inflammatory response(7).

Complications

The complications included acute respiratory distress syndrome(ARDS), arrhythmia, shock, acute kidney injury,

acute cardiac injury, liver dysfunction and secondary infection. The poor clinical outcome was related to disease severity. The disease tends to progress faster in elderly people, with the average number of days from the occurrence of the first symptoms to death was shorter among people aged 65 years or more. Similar to H7N9 patients, the elderly male with comorbidities and ARDS showed a higher death risk. Additionally, more than 100 children were infected, with the youngest being 30 h after birth. Neonates and the elderly need more attention and care due to their immature or weak immune system(2).

In a Norwegian study, the occurrence of sudden acute medical events such as lung and heart failure with dyspnea and hypoxia, sepsis and kidney failure were observed. Concomitant symptoms such as fever, cough and shortness of breath required oxygen therapy especially in people with weak muscles were also observed. About 60% develop bilateral pneumonia with increased mucus production. Hypoxia related delirium, agitation and significant disabling anxiety is seen in people with dementia(3).

Treatment

As prevention is better than cure, the first thing is isolation of the infected individuals in order to curb the further spread of the infection. Mild cases without any history of contact should be managed at home including those with fever and cough. Individuals with discomfort in breath, providing oxygen through nasal prongs, face mask, high flow nasal cannula and use of non invasive ventilators is indicated. At times mechanical ventilator and extra corporeal membrane oxygen support may also be needed. Antifungals and antibiotics are administered if co-infections persist in patients. Antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the experience with SARS and MERS. In a control study on patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes in comparison to those who were ribavirin administered alone. Some of the patients also underwent renal replacement therapy.

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, 76% were given oxygen, non-invasive ventilation to 13%, 4% were on mechanical ventilation, 3% with extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT) in 9%, antibiotics to 71%, antifungals to 15%, glucocorticoids to 19% and intravenous immunoglobulin therapy to 27%. Antiviral therapy consisting of oseltamivir, ganciclovir and lopinavir-ritonavir was given to 75% of the patients. The duration of non-invasive ventilation was 4–22 days and mechanical ventilation for 3–20 days. All children recovered with basic treatment and did not needed intensive care.(4)

Remdeswir, a broad spectrum anti RNA drug developed for Ebola management was not tried for COVID-19, but can probably serve as a better option until tried. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19.

TCM has been used in control of infectious diseases for thousands of years. There is a clear room for the intervention of TCM as a complementary therapy for COVID-19 patients. It is reported that the patients with SARS-CoV infection have benefited from TCM treatment, including controlling the side effect of conventional therapeutics. Based on these factors, there is a general expectation that TCM would be a valuable weapon in the fight against SARS-CoV-2. Consistent with previous analysis, WHO also concluded that to date, there is no

specific medicine recommended to prevent or treat SARS-CoV-2(5).

Conclusion

The current pandemic Covid-19 has challenged the scientific world that unravelling nature's fury is not in the hands of mankind definitely. However, this pandemic serves as an evolutionary force, where the human lives are stake with the heavy death toll globally.As of now scientists around the world are tirelessly working towards the remedy for the Covid-19.

The possible intervention for Covid19 may be approached in a varieties of ways;

1. Blocking the host cell receptor towhich the Viral spike(S) attaches.

2. Deactivation of the receptor that specifically recognises the spike protein after attachment.

3. Possibility of inhibiting the viral RNA using guide RNAs, if possible so that it cannot be translated. As discussed there are 7 RNAs that are produced, of which which we could identify the critical one which is essential and disintegrate. This is similar to antisense RNA technology.

4. Any key step that is triggering the host cell machinery for that aids in viral replication can be targeted.

5.Production of vaccines – Though it is the need of the hour to first get rid of the virus or rather combat the virus at the earliest possible. But as the human race has been exposed to an array of viral infections in the the last couple of decades, the body is exposed to a wide range of vaccines one after the other. A time may come when humans will be consuming nothing natural but everything unnatural or rather man made(modified).

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