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**QUESTION**

Discuss the etiology, origin, structure and pathophysiology of COVID-19.

**ORIGIN**

The name “coronavirus,” founded in 1968, is a family of viruses that got its name from its appearance. The word ‘corona’ means crown. The scientists who in 1968 came up with the name, observed that under an electron microscope, the virus resembled a solar corona; the bright crown-like ring of gasses surrounding the sun that is visible during a solar eclipse. Thereby, giving it the name **CORONAVIRUS**.

The Coronaviruses (CoVs) is a class of viruses. They are large, enveloped positive strand RNA viruses that cause severe acute respiratory syndrome (SARS) with a large RNA genome (with size about 30,000 nucleotides). They are species of virus belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, Roniviridae and Mesoniviridae families. The Coronaviridae family is the largest one of the four families, by its genomic sizes. Coronaviridae virus family is also subdivided into two subfamilies, Coronavirinae and Torovirinae. It is now divided into four genera, Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus. The alpha and beta coronaviruses originate from bats and rodents (it is also the coronavirus that affect man) while the gamma and delta originate from avian species. This classification of Coronaviruses has been based on genomic organization, similarities in genomic sequence, antigenic properties of viral proteins, replication strategies, and structural characteristics of virions, pathogenic, cytopathogenic and physicochemical properties. There are seven different strains of corona virus and they are:

* 229E (alpha coronavirus)
* NL63 (alpha coronavirus)
* OC43 (beta coronavirus)
* HKU1(beta coronavirus)
* MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome- MERS)
* SARS-CoV (the beta coronavirus that causes Severe Acute Respiratory Syndrome-SARS)
* SARS-CoV2 (the novel coronavirus that causes coronavirus disease 2019- COVID-19)

The virus that causes **COVID-19** is designated Severe Acute respiratory Syndrome Coronavirus 2 (SARS-CoV2) formerly referred to as 2019-nCoV. It occurred in December,2019. It started in Wuhan, a city in Hubei province of China. It is the 7th corona virus found to cause illness in humans and it is also a beta coronavirus. Some early evidence suggest that it is transmitted from snakes to humans, but now new evidence is suggesting it more likely came from bats. There is an animal market in Wuhan, that seemed to be the epicentre for this outbreak and it has suggested that their exposure to live and dead animals.

**STRUCTURE**

Coronaviruses are enveloped viruses with round and sometimes pleiomorphic virions of approximately 80 to 120 nm in diameter. They contain positive-strand RNA, with the largest RNA genome (approximately 30 kb). The genome RNA is complexed with the basic nucleocapsid (N) protein to form a helical capsid found within the viral membrane. Coronaviruses encode five structural proteins in their genomes. These includes the Spike (S), Membrane (M), Envelope (E) glycoproteins, Hemagglutinin Esterase (HE) and Nucleocapsid (N) protein. All envelope proteins and N protein is present in all virions but HE is only present in some beta coronaviruses;

1. SPIKE(S)

They are located outside the virion and forms the peplomers on the virion surface, giving the virus its corona or crown-like morphology in the electron microscope. S proteins bind to the virion membrane through the C-terminal transmembrane regions and they also interact with M proteins. The integrity of the envelope is essential for viral infection, and is the Achilles heel of the virus, because the lipid membrane can easily be destroyed by lipid solvents such as detergents, alcohol and some disinfectants. In order to infect a cell, the spikes bind to the cell surface called a receptor (Covid-19 receptor is the Angiotensin- Converting Enzyme2 - ACE2). Host jumping is usually triggered by mutations in spike proteins which change them in a way that they now can bind to a receptor in a new species. Virions can be bound to specific surface receptors in the plasma membrane of the host cell via the N-terminus of the S proteins.

1. THE MEMBRANE (M) GLYCOPROTEIN:

This membrane has three transmembrane regions. They are glycosylated in the Golgi apparatus. This modification of the M protein is crucial for the virion to fuse into the cell and to make protein antigenic. The M protein plays a key role in regenerating virions in the cell. N protein forms a complex by binding to genomic RNA and M protein triggers the formation of interacting virions in this endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) with this complex.

1. ENVELOP (E) GLYCOPROTEIN:

They are small proteins that are composed of approximately 76 to 109 amino acids. About 30 amino acids in the N-terminus of the E proteins allow attachment to the membrane of viruses. In addition, coronavirus E proteins play a critical role in the assembly and morphogenesis of virions within the cell.

1. NUCLEOCAPSIDS(N) PROTEIN:

They are phosphoproteins that are capable of binding to helix and have flexible structure of viral genomic RNA. It plays an important role in virion structure, replication and transcription of coronaviruses, because the N protein localizes in both the replication/ transcriptional region of the coronaviruses and the ERGIC region where the virus is collected.

The genomes of all coronaviruses have a similar structure. The 51 approximately 20 to 22 kb carries the replicase gene, which encodes multiple enzymatic activities. The replicase gene products are encoded within two very large open reading frames (ORFs), ORFs 1a and 1b, which are translated into two large polypeptides, pp1a and pp1ab, via a frameshifting mechanism involving a pseudoknot structure formed by the genomic RNA (25, 116, 178). The structural proteins are encoded within the 31 one-third of the genome, for all coronaviruses, There are untranslated regions (UTRs) on both the 51 and 31 ends of the genome, which are believed to interact with host and perhaps viral proteins to control RNA replication, which includes the synthesis of positive- and negative-strand genomic-length RNA. Also, there are conserved sequences at the beginning of the transcription sites for each of the multiple sub genomic mRNAs; these are called transcriptional regulatory sequences (previously known as intergenic sequences).

**ETIOLOGY**

Coronavirus may have simply evolved from older animal – infecting corona virus. Coronaviruses are huge family of virus species that infect animal cells. Some infect chickens, other infect pigs, some infects humans but most of them are extremely mild. They simply cause common cold.

 Corona means crown refers to the unusually large crown like spikes sticking out of there membranes. This protein spikes are selectively sticky, sort of like Velcro. They don’t attach to most objects but are extremely sticky when they bump into specific molecules found on the outsides of animal cells. Once held firmly in place, the corona virus waits until swallowed by the cell. It then begins to reproduce at the cells expense. Different types of molecules are on the outsides of the cells. Because of this, bird infecting corona viruses usually can’t infect humans, their “Velcro” doesn’t hold enough to our cells. When virus gene are being copied during reproduction, mutations can occur. These are either due to simple copying error, or processes called reassortment and recombination. These happen when two or more viruses infect a single cell. In most cases mutations that change the shape of viral spikes render the virus useless. The Velcro no longer sticks to any host cells. On rare occasions, however, a chance mutation will happen to allow a virus to attach to a new host species. If the modified virus is then lucky enough to encounter that new host species, infection can occur and this is called a **SPILLED OVER VIRUS** and this what happen in coronavirus.

The virus has spilled over into a new type of host. Early on during a spill over event the virus usually isn’t very good at infecting its new host. It Velcro is not a perfect match and many other challenges might slow the virus down. Oftentimes the mutations that let it infect the new host also make it worse at infecting its original host. Because of this, many spills over viruses go extinct after infecting just one or two people, they’re usually dead ends. If the virus can survive and reproduce just long enough, natural selection will promote and new mutations that help it better spread and reproduce in the new host population. Positive mutations accumulate over multiple generations, negative mutations are discarded until a new epidemic occur. Genetic evidence tells us that slowly evolving spill overs have been the cause of almost every major outbreak known in history.

In the early 2000s, a beta coronavirus that used to only infects bats appears to have spilled over into civets. There it mutated even further and spilled over into humans which is then called the SARS virus because it causes Severe Acute Respiratory Syndrome. It spread internationally from person to person. A coronavirus from camels also recently spill over to humans causing even more deaths. Other spill over viruses are: HIV from Chimpanzee, Swine flu from Pigs etc. The novel coronavirus responsible for the coronavirus disease 2019 pandemic, COVID-19 is also a beta coronavirus. The genome of the virus is fully sequenced and appears most similar to a strain in bats, suggesting that is also originated from bats. It is also very similar to SARS coronavirus and is therefore named SARS-coronavirus2(SARS-CoV2).

**PATHOPHYSIOLOGY**

Covid-19 is a virus caused by the virus known as SARSCoV-2. It has a membrane and inside the membrane it has a single stranded RNA. On the surface of the virus we have proteins and sugars. S proteins are also present on the surface of the virus which are basically the key when the virus is inhaled. This virus can be transmitted through respiratory droplets; directly through coughing, sneezing or also through the faecal-oral route e.g. faecal material that has the virus in it ultimately goes into our mouth it goes down into the digestive system and have various effects there. These S proteins are a key that needs to lock into a protein in the body in order for the virus to get into the cell to have its effect.

The alveolar are basically the air sacs within the lungs, so when we inhale something it goes into the oral cavity down the Trachea, bronchi, bronchioles and then ultimately get into the alveoli.

Gas exchange is the primary function of alveoli. There are 3 major cell types within the alveolar and these cell types are called Alveola type 1, Alveola type 2 and macrophages. Sometimes they are called Pneumocyte: type 1 Pneumocyte, type 2 Pneumocyte.

* Type 1 cell is for gas exchange and they have simple squamous epithelia i.e. the type 1 cell is a single layer of squish looking epithelial cells.
* Type 2 cell which have cuboidal epithelia produce surfactant which breaks the surface tension of the water in the alveolar.
* The macrophages are immune cells.

In normal conditions, bacteria or virus do not enter the alveoli because of the mucus and cilia which usually captures particles prior to their entry. However, some bacteria and viruses find their way into the alveoli causing infection to the tissue and this is known as Pneumonia.

 In Covid-19, if the virus enters into the alveoli, the type 2 alveolar cells (the ones that produce surfactant) actually have a protein on their surface and this protein is the receptor which the S protein on the virus surface binds to. This receptor is called ACE 2 (Angiotensin converting enzymes -2). It converts angiotensin 1 into angiotensin 2. The angiotensin 2 increases blood pressure by constricting certain blood vessels. ACE 2 turns angiotensin 2 into Angiotensin 1-7 (AT 1-7) which drops blood pressure by relaxing the blood vessel. It is also anti-inflammatory. ACE 2 has 2 major function it helps to reduce blood pressure and also have anti-inflammatory properties.

When the S protein of the virus binds to the ACE-2 receptor, the virus penetrates the cuboidal type 2 cell. It fuses the membrane of this cell and it releases a single-stranded RNA. When the single-stranded RNA enters the cell, it hijacks the transcriptional machinery thereby producing S- proteins, other surface proteins and sugars and also membrane. They reassemble and take some part of the single stranded RNA which then make the cell burst open thereby releasing the newly formed virus into the alveoli and this leads to irritation. This irritation can lead to coughing and when an individual cough, the virus is expelled out into the atmosphere in respiratory droplets which facilitate further spread.

When the cells release the viruses into the alveolar, they also release a whole bunch of chemicals (pro-inflammatory chemicals) E.g. cytokines which includes the interleukins and the tumour necrosis factors. The cytokines make the blood that goes past the alveolar more permeable or porous i.e. the blood that pass starts to leak out. The plasma also leaks out between the blood vessel and the alveoli, but it also goes into the alveoli which means instead of oxygen and carbon dioxide crossing the very thin barrier it is the plasma that crosses which makes the barrier thicker. Making it hard for gas to go back and forth because there is now fluid(plasma) in it. This fluid then stops the gas exchange thereby causing **Acute Respiratory Distress Syndrome**.

 In addition, to make the alveola more permeable, the blood vessel gets wider and more blood comes thereby resulting in **Localized Inflammation**. But in severe cases, the inflammatory chemicals can enter the blood stream and go to the whole body resulting in **Systemic Inflammation**. This systemic inflammation could result in **Septic Syndrome** which means the individual has inflammation around the entire body. When there is inflammation around the entire body, it affects all tissues and organs which then leads to **Organ Failure**. Also, WBC comes in the alveolar e.g. Neutrophils. This can lead to Pus being formed and this causes thickening of the alveolar barrier making it harder for gas to exchange. Because the type 2 cells are affected less surfactant are produced which means the alveolar are more likely to collapse which can lead to **Fibrosis** over time.

When the cytokines are in the blood stream, they can also go to the brain specifically the hypothalamus which regulates body temperature. These cytokines cause an **Increase in the Body Temperature.**

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