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New Variant of Corona Virus and its Crosstalk with Alzheimer's Disease

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Abstract

Being a pandemic disease as declared by WHO, Corona virus disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov-2) has become the major reason for death of people worldwide. This article provides a glimpse of the symptoms caused by the invasion of virus, structure of the virus and conveyance of the virus from infected person to healthy individual and some of the new strains which have been detected recently. Alzheimer's disease causing dementia is another co-morbidity causing death of covid-19 patients, correlation between these two fatal diseases is grabbing attention of scientists in various parts of the world. This study shows the interaction of Covid-19 with Angiotensin converting enzyme 2 (ACE2) receptors lead to stimulation of neuroinflammation which paves the way towards the progression of Alzheimer's disease. As Apolipoprotein E4 (ApoE4) gene possessing people are susceptible for Alzheimer's disease pathologies, similar susceptibility has been found in SARS-Cov-2 invasion. Cytokine storm stimulated by SARS-Cov-2 virus is also involved in the exacerbation of immune responses in CNS by over activating the brain cells including astrocytes and microglia. These events lead to neuroinflammation and eventually progress the Alzheimer's disease condition. As the disease is posing serious burden on global health, getting an insight into the disease to develop new treatment and prevention strategies are of utmost importance for the scientists all over the world.

Keywords: *Covid-19; Alzheimer's Disease; New Strains; B117; B1351*

Introduction

The widely spread pandemic disease known as corona virus disease: Covid-19 occurs via the infection of Severe Acute Respiratory syndrome corona virus 2 (SARS-Cov-2). The virus has a crown like structure due to the presence of spike proteins on the outer surface of the virus [1]. The main protein constituents of the virus are envelope glycoprotein, spike protein, membrane glycoprotein and nucleocapsid protein and some other crucial proteins required for the growth and replication of virus (Figure 1). Spike proteins help in viral entry inside the host by binding with the Angiotensin converting enzyme 2 (ACE2) receptors. These spike proteins contain two subunits S1 and S2. S2 subunit is involved in the fusion of virus and S1 subunit possesses receptor binding domain [2]. First report of corona virus in India was seen in Thrissur district of Kerala on January 2020. By March 2020 the disease was proclaimed as pandemic by the World Health Organization (WHO). New strain of SARS-Cov-2 with mutated spike protein was detected in December 2020 in the UK.

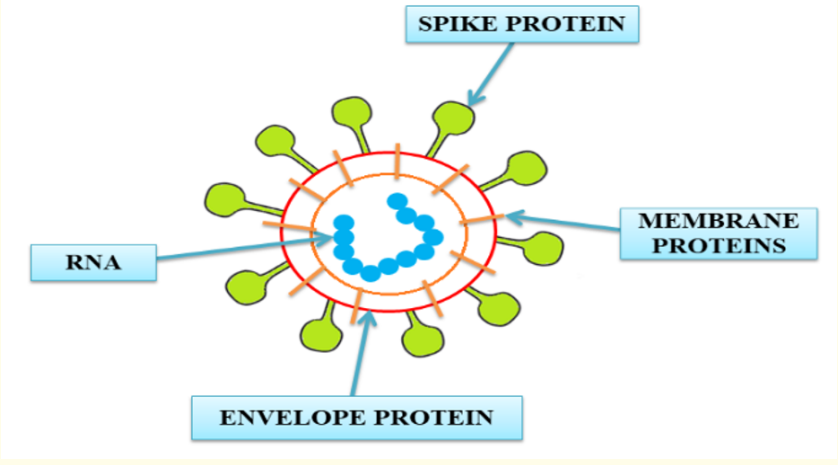

Figure 1: *Structure of corona virus. The basic structure of corona virus containing the spike proteins which give it a crown like structure and helps the virus to gain entry inside the host cell by binding with the ACE2 receptors. Other proteins of the virus are envelope proteins and membrane proteins. It is a single stranded RNA virus which can also be seen in the figure.*

Transmission of the virus occurs via various modes. Generally, corona virus gets passed on from one person to another via respiratory droplets or contact with the infected person. When an invaded person sneezes or coughs, the discharged droplets which are > 5 - 10 µm in size, enters into the person who is in close contact with the infected person at a distance of 1m via mouth, nose or eyes. Indirect transmission of the virus loaded droplets can also occur via fomites, immediate environment around the infected person, when a healthy individual touches the contaminated object [3] (Figure 2). Other possible routes through which corona virus gets entry inside the human body and transmission via various routes are shown in table 1. Transmission by asymptomatic carriers has also been reported [4-6].

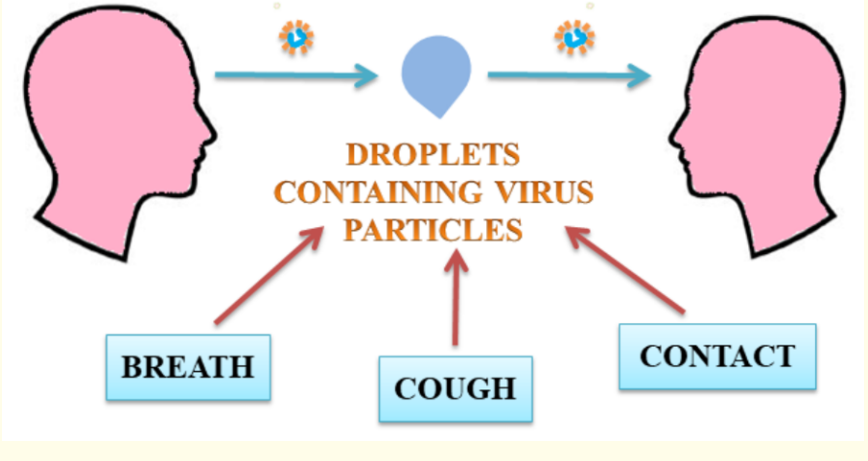

Figure 2: *Transmission of corona virus via droplets from infected person to normal person. The viral particles discharged by an infected person while coughing or sneezing enter the normal person via the discharged droplets containing the virus or by coming in close contact with the infected person.*

Routes of entry of corona virus	Transmission modes of corona virus	
Nasal route	**Direct**	**Indirect**
Axonal transport	Respiratory droplets	Fomites
Lamina cribrosa	Sneezing, coughing	Air borne transmission
Neural parenchyma	Close physical contact	Fecal route
Olfactory bulb		

Table 1: *Transmission and entry of SARS-Cov-2 inside the human body.*

The main symptoms of Covid-19 along with some less usual symptoms are shown in table 2 [7,8]. As far as the risk factors for the disease are considered, age is the most prevalent one according to various reports and studies. Other risk factors include cancer, respiratory and cardiovascular disorders like hypertension, diabetes, lung diseases, etc. Smoking and obesity also account for greater risk of Covid-19. In some reports men were found to be more affected than women this may be due to increased smoking habits in men than women and other co-existing diseases [9].

Primary symptoms	Secondary symptoms
Fever, Fatigue	Abdominal pain
Loss of sense of taste and smell	Diarrhoea
Dry cough	Nausea
Myalgia	Vomiting
Dyspnea	Headache

Table 2: *Symptoms emerging following the invasion of SARS-Cov-2.*

As HIV patients are already lacking proper functioning of immune system and other manifestations they can become a potential target for Covid-19 infection which can come out to be a syndemic and may increase the burden of disease in those patients. But there is very limited data for co-infection of HIV virus and SARS-CoV-2 because the patients with HIV are subsequently receiving antiretroviral therapy which can provide them some prevention towards Covid-19 [10]. Pregnant women and neonates are more liable to the invasion by virus because various physiological and mechanical modulations are seen during pregnancy. Fetal complications due to COVID-19 may count miscarriage, intrauterine growth restriction, and premature birth [11].

Methods of collection of data

The screening of papers was conducted online by using various databases such as PubMed and Google scholar.

New strains of COVID-19

Several new strains of the corona virus has been detected which are able to spread more rapidly in comparison to the earlier strain of the virus making it difficult to control the viral transmission. Viral spike protein mutations have led to the emergence of new strain known as UK B.1.1.7. lineage also known as VUI202012/01 which has higher affinity for the ACE2 receptors and increased interaction between host cell receptors and virus. This leads to increased levels of virus inside the host cell and enhancement in its transmission from infected person to a healthy individual [12]. The B117 lineage spike protein harbors 8 mutations out of which N501Y mutation is within

the receptor binding domain, three mutations ΔH69/V70, A570D and ΔY144 are in S1 region, and four mutations, S982A, T716I, P681H, and D1118H are in S2 region. [13]. Another mutant strain is B.1.351 lineage having mutation in the spike protein. It also has increased transmissibility similar to B117 and has become the dominant strain among all [14]. The B117 strain possesses 99% similarity in protein to the original strain therefore there was no increment in the disease severity and death than the original strain of the virus. This suggests that due to very minute difference in the protein content of the virus the vaccines generated are still effective even against the new strains [15] (Figure 3).

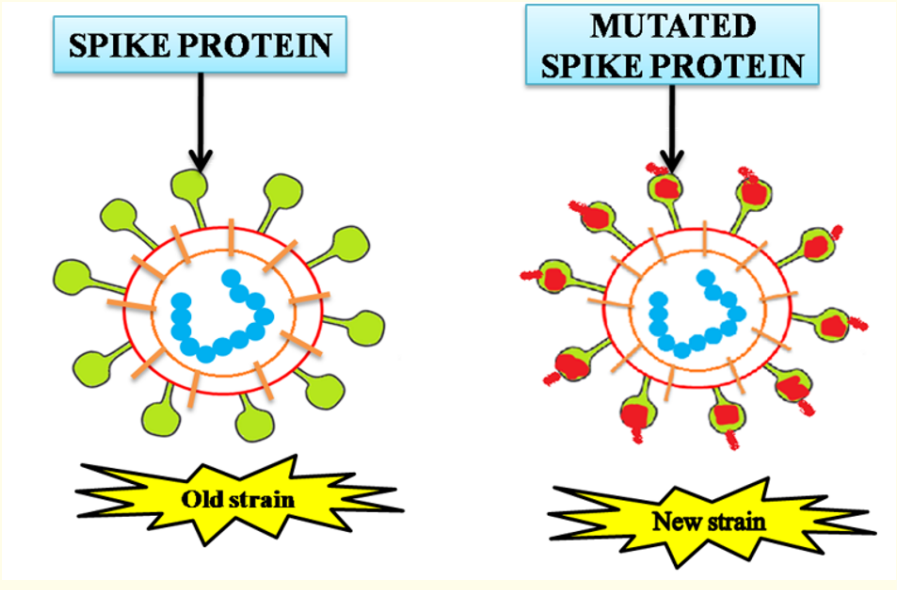

Figure 3: *New strain of SARS-Cov-2. Shows the new strain of SARS-Cov-2 having mutations in various sites of spike protein which helps in the entry of virus inside the host cell by binding with ACE2 receptors. This favors the rapid transmission of new strains in comparison to the old ones.*

Interplay between Alzheimer's disease and Covid-19

Alzheimer's disease patients are more prone to Covid-19 infection. This is due to poor memory, inability to get involved in physical activities and unwillingness to perform any routine tasks, which makes the Alzheimer's disease patients to follow the prevention guidelines given by healthcare authorities for Covid-19. Along with this, behavioral and psychological symptoms doesn't allow them to continue isolation [16]. Neuroinflammation is the major factor responsible for the neurodegeneration in Alzheimer's disease. Older age people are more susceptible to the invasion of SARS-Cov-2, this is due to the increased inflammatory baseline in elderly people which is often termed as inflamm-aging. Due to hyperactive immune system of the body caused by Covid-19, inflammation also occurs in brain regions leading to neurodegeneration and gradually progresses Alzheimer's disease condition [17]. SARS-Cov-2 is having neurotrophic characteristics which aid it to invade the neural tissues via axonal transport, neural parenchyma, olfactory bulb and nasal mucosa. The SARS-Cov-2 binds its spike proteins to the ACE-2 receptors present in the glial cells and neurons. It affects the cardiovascular activities regulating regions of CNS as well as stimulating inflammatory responses by causing astrogliosis and activation of microglia along with other inflammatory mediators promoting neuroinflammatory cascade contributing in AD progression [4] (Figure 4).

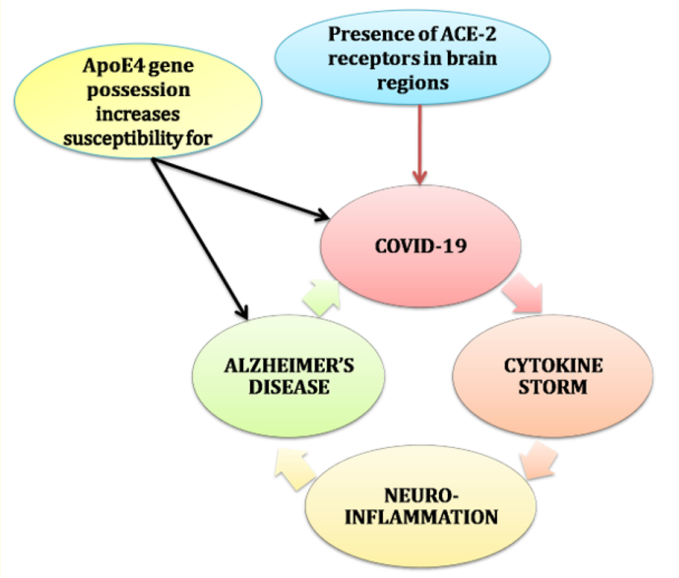

Figure 4: *Crosstalk between Covid-19 and Alzheimer's disease. This figure shows the interrelation between the two diseases. Covid-19 invasion leads to the stimulation of cytokine storm by activating various inflammatory mediators which trigger neuroinflammation cascade promoting Alzheimer's disease. Further the covid-19 virus binds preferentially to ACE-2 receptors which are abundantly present in the brain cells leading to increased invasion of the virus into the neuronal cells. The possession of Apolipoprotein E4 (ApoE4) gene also increases the susceptibility of getting infected by the virus and Alzheimer's disease as well.*

COVID-19 and neuroinflammation in AD

Alzheimer's disease is a common neurodegenerative disorder which leads to progressive loss of cognitive functions and ultimately to dementia. There are several hypotheses claiming to be the cause of the disease but the exact cause of the disease is still unknown. Several factors considered to be involved in the progression and development of the disease are amyloid plaque formation, intracellular hyperphosphorylated tau accretion, cholinergic insufficiency, oxidative stress, neuroinflammation and change in homeostasis of certain metals involved in the functioning of brain like zinc, iron, etc [18]. Covid-19 is related with increase in the immune response of the body and inflammatory processes which can lead to neurodegeneration accelerating the risk of Alzheimer's disease. SARS-Cov-2 infection is associated with the stimulation of cytokine storm which activates various pro-inflammatory markers like interleukin1 and 6 and tumor necrosis factor α (TNF-α) which have been found to be dramatically increased in the elderly people. These manifestations caused by SARS-Cov-2 overlap with the pathogenesis of Alzheimer's disease [17]. Mast cells are involved in innate immune responses of the body and also play a major part in neurodegenerative diseases. Mast cells are having both protective and damaging effect in the body. As corona virus enters via nasal route the mast cells present abundantly in nasal and respiratory tract get activated as a part of immune response of the body. In response to this the mast cells further release pro-inflammatory cytokines and chemokines in the body and CNS along with histamine and proteases and activate astrocytes and microglia exacerbating the immune response. These all inflammatory events eventually lead to the stimulation of cytokine storm and AD type pathologies [19].

COVID-19 and ACE2 receptors

ACE2 receptors are the primary target of SARS-Cov-2 for getting entry inside the host cell. CNS highly possesses these receptors which are located in different regions including brain stem; cardiovascular function regulatory region and capillary endothelium. Other than these routes SARS-Cov-2 can also use trans-synaptic olfactory bulb route for getting inside the host. When the host gets invaded by the virus in the brain region, the virus stimulates the brain cells and result in astrogliosis, microgliosis and enhanced inflammatory cascade in the brain. Due to systemic invasion by the virus there occurs disruption of blood brain barrier and ultimately neural damage takes place causing death of neurons. The neuroinflammation further destroys the hippocampal and cortex functions and leads to neurodegeneration and Alzheimer's disease [4]. According to some studies it has been proved that increment in ACE2 receptors due to some drugs targeting ACE2, increases the levels of nitric oxide in the brain. In normal physiological conditions, nitric oxide shows neuroprotective and immunomodulatory effects but when the levels of nitric oxide get significantly increased it causes neurotoxicity and play a part in the progression of Alzheimer's disease. The brain cells including astrocytes, microglia and macrophages derived from blood are also responsible for the stimulation of inflammation by releasing nitric oxide and they are also responsible for triggering the generation of amyloid β, a pathogenic hallmark of AD [20].

COVID-19 and ApoE4 gene in AD

Apolipoprotein E4 (ApoE4) allele is considered to be responsible for the late onset Alzheimer's disease (LOAD). People inheriting this gene are at greater risk of Alzheimer's disease, possessing this gene makes them suffer early memory loss and cognitive function than those who are not having the gene. ApoE4 gene is also related to the increased accretion of amyloid-β plaques which eventually leads to disruption of synaptic plasticity and hinder the signal transduction process contributing in AD pathologies [21]. ApoE4 gene containing people are highly susceptible to viral infections therefore those people are at increased risk of getting invaded by SARS-Cov-2. Other isoforms of ApoE are ApoE2 and ApoE3 out of which ApoE2 plays protective role. The major producers of ApoE are the astrocytes, however, neurons and microglia can also produce it which is then released into the extracellular space. It can also cause damage to the blood brain barrier by destroying the brain capillary pericytes which are responsible for maintaining the integrity of this barrier. However, it is still unclear that whether cerebrovascular effects due to ApoE4 are responsible for cognitive dysfunctions or not [22].

Conclusion

Covid-19 as a result of invasion by the SARS-Cov-2 virus has posed a serious problem on public health leading to death of people worldwide. Better understanding of the viral structure, entry, transmission and strains is crucial for aiding the development of proper treatment and prevention strategies for the disease. This review summarizes the structure, transmission, risk factors and symptoms of the viral invasion along with the basic features of the new strains of SARS-Cov-2 including B117 and B1351. These strains have mutated spike proteins which increase the viral binding with ACE2 receptors and promote rapid transmission of the virus. People with diseases compromising the immune system of the body are at greater risk of getting infected with the virus. Some studies have also proven the correlation between Covid-19 and Alzheimer's disease, the major cause of dementia leading to neurodegeneration. Covid-19 stimulates the cytokine storm by interacting with various inflammatory cells of the body and CNS which further lead to astrogliosis and microgliosis causing neuroinflammation. This leads to the progression of Alzheimer's disease. SARS-Cov-2 increases neuroinflammation also by binding with ACE2 receptors present in the neuronal cells. Along with these people possessing ApoE4 gene, a risk element for Alzheimer's disease, are also susceptible for invasion by SARS-Cov-2. The interactions between the diseases suggest that the diseases can affect the progression of one another via various pathways. These all findings can aid in the development of proper treatment strategies for both the diseases.

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