Interlinking the Happenings of the Pandemic Cases of COVID-19 with the Prevailing Neurological Disorders

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Abstract: **This article is designed to visualize the repercussions caused by Covid-19 on the neural system. The deadly virus has devastated the earth with its worst effects claiming millions of lives. Neurological demonstrations are another important aspect that needs attention for the current situation. Relating COVID-19 to the mechanism of the system that makes up the nervous control display the latent indulgence of the virus in attacking hosts system. Thus, coronavirus invasion is worst as it can cause both breathing as well as neurological destructions via distinct allies. Formerly, the neurological obstacles were not identified in Covid patients, later investigations revealed that it has an injurious impression on the working of CNS leading to prolonged illness.**

The aged people are at an extensive risk due to deviations in the mental status and stress. Viral infections here are alone enough to induce toxicity and conquer the neural network of the attacked individual. The coronavirus has destroyed the mankind to roots, making it difficult to treat. Scientists report that SARS-CoV-2 is not only inimical in distorting the breathing channel but also worsens the neurological health leading to chronic disorder.

Patients suffering from COVID-19 require persistent care as it reluctantly injures the body system. A relevant treatment for the infection is not yet discovered. Without vaccines, this virus seems impossible to defeat. Some analyzers are in a race to accomplish an adequate vaccine, and the trials are still in progress. The pathological effects of COVID-19 control the entry and the virus replication, which will be also discussed.

The methodology used for the above findings will include the analysis of review articles, database and different scholar sites. Various images will support the text for enhanced understanding. Scientifically precise report with the verified findings is the motive. Covid-19 is the hot topic of research nowadays, which requires an elementary apprehension starting from the scratch covering all major aspects. An overview on the pathogenesis, possible neuroinvasive mechanism and control practices for CoV infections with neural system involvement will be provided.

Keywords: **Neuroscience, COVID-19, Neural Disorders.**

1. Introduction

In a world population of 7.8 billion people, the killer virus has already contaminated approximately half of them, affirming 467,000 deaths as of June end and threatens to claim many more. World Health Organization proclaimed this instantaneous wave as universal pandemic on March 11, 2020. The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a novel coronavirus that is accountable for causing a lethal viral infection COVID-19 [1], [2]. The existing situation has placed the world in dilemma, because it is traumatizing everyone to no end. The 1918 Spanish flu was the most severe pandemic, and the mistakes committed by humans should not be repeated today. The influenza spread lasted 2 years at the time when technology was not much advanced. Today, the revolutionary expansion of digital world makes examination simplified.

The destruction started in the streets of Wuhan, China has escalated globally and is deteriorating with time. The SARS-CoV-2 is an advanced coronavirus that is a representative of the *Coronoviridae* family and is supposed to be zoonotic as it is depicts genetic uniqueness to bats. There are diverse parameters for clinical control that are in need of optimization [3]. The monster virus, starting from the respiratory tract to further gastrointestinal channel, finds its home even in the cerebrum infecting hosts cells ending in death. Middle East Respiratory Syndrome (MERS) is caused by MERS-CoV that is another version of coronavirus which was reported in Saudi Arabia for the first time. Reports suggest that another variety also had the capability of distorting the CNS causing neuro-related illness other than respiratory ailments.

The SARS-CoV-2 patients show major respiratory symptoms, including pneumonia, fever, breath shortness, headaches, chest ache, loss of taste, skin rashes, sore throat. But doctors have also noticed an array of neurological symptoms and that too specifically in the aged people who have some severe medical conditions (diabetes, bronchitis). Not many cases are recorded but has adverse effects if happens to invade the brain.

2. Genetic Structure of Covid-19 and Inclusive of Covid-19 Pathogenesis

The current international virus is reported to have a spike head resembling a coronet with a +ve stranded RNA genome. SARS-CoV-2 illustrates anatomical similarity with the original SARS-CoV-1 virus which was responsible for 2002 infestation. The virus assault is initiated when the s-proteins carrying the receptor holding domain allows it to attach to the host

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membrane. The ACE 2 residing in the bronchi, heart and kidney affixes with these s-proteins initiating the disease. This devil virus is ten times more active in seizing host cells than the original virus [4], [5]. The m-protein i.e. the membrane protein on the upper portion interacts with the different peptide-structure, that accountable for the coronavirus synod. E-protein is the tiniest of all and manages intercellular exchange which resides in ER and Golgi bodies. The capsid sits behind the viral coating which includes the genetic material of virus. The N-protein (nucleocapsid protein) aids the viral RNA for its replication [6].

A. COVID-19's Entry and Replication

Studies conducted release that the virus proliferation takes place by respiratory droplets which permit them to enter the nasal lane. Within the mucosal epithelium of loftier respiratory tract, the viral cloning occurs. The s-proteins are bisected by the proteases discharged by the host cells after its binding to the ACE 2 receptors. This turns on the protein for membrane integration before insertion of its genome into host cells [7], [8]. Moreover, this viral cell approach via endocytosis can also happen for enhancing the specific-viral cell entry into cytoplasm. The supplementary proteins are generated which guides the designing of glycoproteins. The matured virions are hence gathered by fusing to the plasma membrane, here an inter play of host cells within viral cells end up in cell apoptosis. Various inflammatory mediators, extricated at the time of cell disruption, mucus built up causes hyperplasia in cells [9], [10]. This inflammation is responsible for irritation in cell lining airways leading to cough. Going down, in the respiratory channel within lungs the virus follows the path of trachea, bronchi and alveoli.

Recent studies convey the issue of slight mental health alterations in some COVID patients displaying symptoms like anosmia and ageusia simultaneously stipulating a neuroinvasive identity of virus.

B. Cytokine Storm and ARDS

The alveolar tenderness impairs its ability of interchanging gases and gets packed with fluid emerging respiring problems. In few persons, the procedure of cellular infection of SARS-CoV-2 virus develop the immune response and liberate pro inflammatory mediators causing what is called as Cytokine Storm or Cytokine Release Syndrome. Cytokines are proteins that conduct cell signaling and supervise other immune retaliations. A large amount of pro inflammatory cytokines (IFN-α, IFN-1ß etc.) and chemokines (CCL-2, CCL-3 etc.) are released as feedback [11]–[13]. The Lancet, reports shows that this cascade of inflammatory mediators causes an uncontrolled systematic immune response which conduct to Acute Respiratory Distress Syndrome (ARDS) which generates rapid inflammation in lungs and causes epithelial and endothelial cells of lungs to secrete inflammatory mediators which fills the alveoli. This can trigger major immune responses that can cause various body parts to fail and ultimately demise [11].

In addition, these inflammatory signaling cells recruit other cells of immune system into the alveoli which further amplify the problem. Additionally, the systematic inflammatory state causes capillary permeability which results in even more fluids entering the alveoli. Overall, this pathology severely impairs the capacity of the lungs to exchange oxygen and carbon dioxide as it has now become filled with fluid and inflammatory mediators [14].

C. Immune Evasion by SARS-CoV-2

Since the viruses use various tactics to stay in host cells and at same time bypass immune responses. Study says that, the transformed microbial structures called Pathogen Associated Molecular Patterns (PAMPs) can be apprehended by Pattern Recognition Receptors (PRRs). However, this lethal virus can affect the making of double membrane vesicles that has absence of the PRR and then gets duplicated in these vesicles, escaping the host recognition of their dsRNA. IFN-I (IFN-α and IFN-ß) has a shielding effect on virus infection, but the IFN-I track is obstructed in infected mice [15], [16]. Accessory protein 4a of virus may inhibit the initiation of IFN at the level of MDA5 simulation through direct communication with double stranded RNA. Besides, ORF4a, ORF4b, ORF5 and the membrane protein of virus obstruct nuclear transport of IFN regulatory factor 3 (IRF3) and simulation of IFN β promoter. The coronavirus can also affect the Ag presentation. Hence, ruining the immune evasion of SARS-CoV-2 is crucial in its therapy and particular drug development [9].
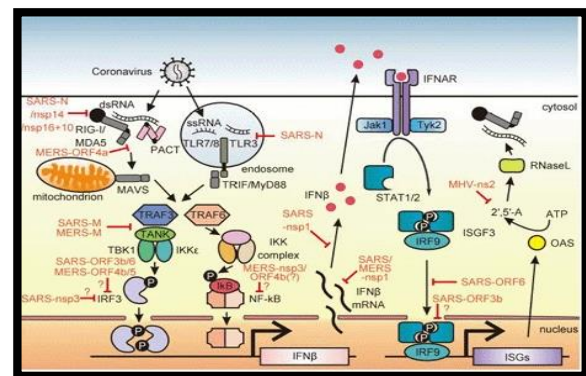

Fig. 1. SARS-CoV-2 Immune evasion

3. Neurological Interlinking of COVID-19

The fresh documentation, propose that CoV altered physiology also entail the neural process. Reports from China with 200 above candidates reporting Covid infections also face neurological signs. They comprise diminished responsiveness, drastic cerebrobasilar malady and skeletal muscle disfigure trait, indicating the participation of both CNS as well as PNS. The mentioned symptoms are highly probable to happen in victim possessing preexisting health conditions [17]–[19]. The linking of these neurological indications and the sufferer results weren't scrutinized. Experimenting another study, approx.

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dozen of Covid patients the ailment was led by acute cerebrovascular disease, including ischemic stroke, cerebral venous sinus thrombosis and cerebral hemorrhage.

A relative record in France reveals that 58 CoV patients were hospitalized complaining that they possess ARDS. Out of them, 84% showed neurological signs at different stages of time, from getting admitting to operation theatre till ceasing of neuromuscular barrier. The neural traits encompassed affirmation of encephalopathy, flawed corticospinal stretch, disconcertment with hysteria. The diagnostic results divulged leptomeningeal augmentation and bilateral frontotemporal hypoperfusion with two tainted proofs critical ischemic stroke. Array of diseases are observed versioning from Guillain-Barré syndrome to dire hemorrhagic pernicious encephalopathy in COVID-19 sufferers [17].

In the previous corona virus epidemics, variety of neurological alliances formed was comparatively very less. The test records of SARS patients have registered the development of fits, myopathy and rhabdomyolysis. An experiment included data of 206 SARS infectants depicted 5 of them were bearing acute cerebrovascular disease.
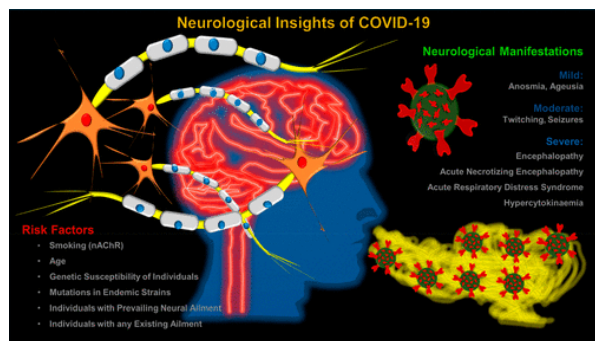

Fig. 2. Neurological perspective of COVID 19

A. How CoV infection destroys Nervous System

Limited studies on the topic have occurred, which suggests different potential mechanism pathway that directs neurological symptoms in the diseased persons.

1) Direct Invasion

The brain marks the existence of the transmissible viral material along with the proteins indicating uninterrupted nervous system bruise hence, distortion.

2) Blood circulation route

An instance of the classic virus that makes its way into CNS via gore is the JE virus, which replicates itself in the tissue cells of the region hit by insect bite. It is eventually liberated into the blood stream to generate mononucleate phagocytes in the skeletal arrangement. Further release may raise the absorptivity of the blood-brain obstruction through the generated cytokines, aiding the virus to enter the cerebrospinal fluid and give rise to encephalitis. Although, it is infrequent that SARS-CoV-2 seizes the neural function by blood circulation, upcoming reports may provide attestation for the same [20].
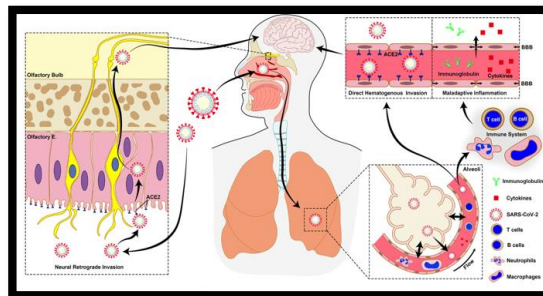

Fig. 3. Potential Mechanism responsible for causing neurological disorders

3) Neuronal Passage

For the neurotropic virus to enter the CNS, neuronal passage is the main carrier. Virus can travel by contaminating the sensory or motor nerve closings attaining reverse or forward neuronal transfer via the proteins, dynein and kinesins. Olfactory neuron trafficking is an instance of neuronal passage. The location of olfactory nerves and bulb in the nasal cavity and anterior brain efficaciously makes it a medium between nasal epithelium and the CNS. Therefore, in prior stages of infection or nasal vaccination CoV can make its way to the brain via olfactory tract. Within 7 days of nasal cell manifestation, it can capture the complete brain and cerebrospinal fluid via olfactory nerve and bulb & can be a source of demyelination and inflammation. It is seen in mice that if the olfactory bulb is eliminated, the capture of CoV into the CNS was moderate [21], [22]. A scholar observed SARS virus molecules and genome sequences in the brain neurons. From the above extract we can conclude that CoV can capture CNS by the periphery via neuronal passages.

4) Hypoxic trauma

Virus replication in lung tissue cells, it gives rise to alveolar and interstitial provocative exudation, edema and growth of pellucid membranes. This in return leads alveolar gas interchange ailment giving rise to hypoxia in the CNS, raising anaerobic process in the power house of brain cells. The collection of acid can lead to cerebral vasodilation, enlargement of brain cells, interstitial swelling, blockage of cerebral gore slide and neuralgia due to inadequate blood supply & clogging [23], [24]. Cerebral edema & circulation ailment will get worse if the rate of hypoxia continues to increase. The working of the brain moderately degenerates causing fatigue, bulgy conjunctival hydrops and even stupor due to intercranial hyperpiesia. Hypoxia injury thus claims neural damage.

5) Immune invasion

The viral illness leading to neural damage may be mitigated via the immune system. The tenacity of SARS-CoV-2 infections plus its capacity to contaminate macrophages, microglia, and astrocytes in the CNS are specifically important. Neuroinvasive virus can trigger glial cells, and instigate pro-agitating condition. The interleukin IL-6 member to cytokine storm is optimistically interlinked to the vastness of novel coronavirus signs [25]. Moreover, huge quantity of agitating

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attributes like as IL-6, IL-12, IL-15, and TNF-α are released when primary glial cells are incubated. Hence, terrible inflammation and cerebrum destruction will be the consequence of immune cell actuation [17].

6) ACE 2

Human brain cells expel the Angiotensin Converting Enzyme 2 on its surface. This protein participates in maintaining BP as well as is binding receptors that facilitates the entry of the virus and pollute cells. It is also spotted on the endothelial cell lining. This permits the virus to follow the breathing track and then the blood pathway to infect further [21]. Finally, it reaches the blood brain barrier. When in brain the virus starts multiplying leading to neurological disorders.

4. Neural afflictions related to CoV infections

A. Viral encephalitis

This condition points out to the provocative injury in the brain parenchyma fostered by parasite, incorporating neural destruction as well as nerve tissue lesions. It is distinguished by critical arrival, where general prodrome includes neuralgia, pyrexia, puking, spasm and alertness disorders. Prior diagnosis is a bit difficult. A treatment team in China confirmed COVID-19 genome sequencing patterns and thereby affirming its presence in brain of patients who are infected [14]. Other records indicate that the cytokine storm results in neural inflammation which causes strokes and makes patients more prone to the mental disorders.

B. Infectious lethal encephalopathy

It is an agitated brain blocking syndrome characterized by traits like hypoxia, metabolic alterations, system's sepsis in the acute infection. It latently attacks the brain, without an evidence of inflammation. It possesses complex symptoms, hard to interpret. CoV patients are the major prey for the virus causing this disease as they suffer from hypoxia as well as viral presence [26]. Moderate number of patient's complaint of headaches, consciousness problem and other brain related symptoms that show up in toxic encephalitis.

C. Severe cerebrobasilar disorder

Massive finding indicates that the viral respiratory tract diseases are alone enough as a factor to cause neural disorder. The current virus is majorly responsible for causing cytokine storm syndrome, which is responsible for improper brain functioning. When the virus attacks the host, platelet reduction happens and an increase in D-dimer occurs that makes a person more susceptible to the disorder [27].

D. Brainstem Dysfunction

The respiratory failure in Covid patients may be linked to the brain dysfunction, studies suggest. The virus when studied in an animal model points out aiming the brain stems neurons that ultimately leads to death [28], [29]. This brain region performs basic physiological respiratory and cardiac processes. Major symptoms include loss of sensation in olfactory receptors.
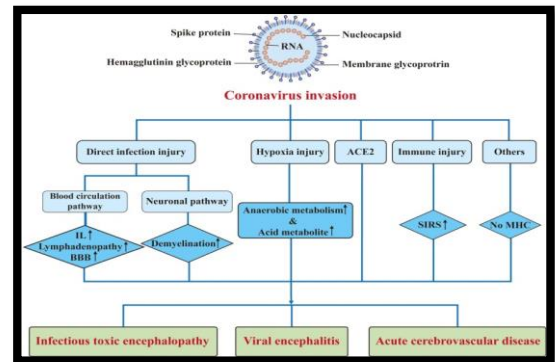

Fig. 4. Nervous system damage caused by coronavirus

5. Diagnosis of COVID-19

According to the World Health Organization, 2020 the tracking of virus by its detection becomes an important task for the diagnosis. Study says that the diagnosis of this disease depends on the clinical manifestations, epidemiological spread and some science-based techniques like PCR, RT-PCR, CT-scan, ELISA and blood culture. As this disease may show asymptomatic signs, therefore it becomes necessary to test via the science-based techniques. The following section will guide through the diagnostic approaches accounted yet for detection.

A. Various diagnostic tool approaches

1) RT-PCR test

A nuclear derived method is used to derive the genetic material from any pathogen. The Reverse Transcriptase PCR utilizes the virus nucleic Acid and hence is used for diagnosis. Chinese Centre for Disease Control and Prevention shared the genetic sequence of SARS-CoV-2 on January 12, 2020. This enabled designing primers against the virus and thus used RT-PCR assay. This technique has become a gold standard for the diagnosis, but is 66-80% sensitive. It means it may reveal negative results although 20-34% in 100. The discrepancy of the results can be due to the variation in the kits, improper sample collection or not so advanced technology for detection of NA. The sample taken is the nasopharyngeal or oropharyngeal swab. The viral RNA is converted to DNA using primer with enzyme Reverse Transcriptase. The DNA amplification then depends on real time PCR using a fluorescent dye or the probe. If the targeted RNA region becomes amplified in the results using fluorescence this brings out the positive results. Contrastingly when there is no amplification that is no targeted region shows that the results are negative. Mostly, SYBR green probe is used in the process which makes it a cost-effective technique.

2) CT- Scans and Laboratory Examinations

For the detection of COVID-19, although RT-PCR is certain, its false negative rate cannot be neglected due to severe outcome of missed diagnosis. Therefore, many healthcare workers suggested CT-scans should be an essential auxiliary detection method because it is more delicate. For persons with high doubt of the current virus infection with negative RT-PCR

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screening, a union of repeated RT-PCR tests and chest CT-Scan may be useful[30], [31]. Pneumonia becomes a difficulty here, which can be exactly resulted using thin slice chest computed tomography relying the final results on RT-PCR [32]. A report suggests that the findings from the cases registered which showed unusual results were admitted in ICU, later exhibited divisional reduction along with feature of bilateral ground-glass opacity (GGO) [31], [33]. The imaging abnormalities of infected patients revealed interstitial swellings, multiple lesions, visible outer pleural distribution along with bilateral GGOs. Furthermore, these results may coincide with other viral pneumonia RT-PCR analysis becomes more essential for accurate outcome.

6. Diagnosing Neural Disorders in COVID-19 Patients

A. Predicting factors

Getting acquainted with the pre-existing brain history of the patients can help. Patients exhibiting some underlying medical conditions and stress related disorders are at a probable risk.

B. Checking Auditory Responses

Auditory brainstem response is a toolbox of ICU and is used to detect the disorder since SARS-CoV-2 not only affects the respiratory tract but also the olfactory as well as auditory pathway. Hearing loss might be observed in the patients which is helpful in assessing the dysfunction.

C. Imaging tools

Brain provocative process is not easy to detect and point. In acutely diseased patients, lumbar rupture could be done to calculate the cytokine extent in CSF. This is a bit complicated technique. Specified Magnetic Resonance imaging would help in detecting same.
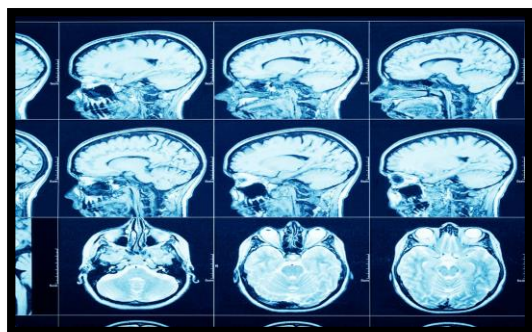

Fig. 5. COVID patients depicting neurological symptoms

7. COVID-19 ongoing Treatment

Presently, there is no successful medicine for curing patients. Moreover, there is no particular antiviral medicine or vaccine for this virus. Finding helpful medication for healing the ongoing outbreak is essential. There are diverse feasible treatments methods like:

1. Increasing ACE 2 expression by injection of soluble recombinant protein or using therapeutic vectors expressing high levels of enzyme which may be relevant in the future
2. Using specific ACE blockers such as lisinopril
3. Obstructing Ang II receptors. In specific, the type I Ang II receptor has been reported to promote disease by encouraging edema and disrupting lung function. Hence, a type I Ang II receptor blocker (example-Losartan) has been successively examined for improving covid-19 pneumonia.
4. Convalescent therapy and other medications like Hydroxychloroquine, Ivermectin and Azithromycin are used.

8. Conclusion

SARS-CoV-2 is not special in being respiratory virus that affects brain. Influenza, measles and respiratory syncytial virus also perform the same task thereby causing neurological disorders. The seasonal coronavirus, HCoV-OC43, spawns mild respiratory signs but can also be source of encephalitis in beings. Likewise, the MERS and 2003 SARS causing virus can be the root of serious neuro disorders.

As per the researches, neurological association is a major factor for the sickness but this view is underestimated due to less proof. Ongoing studies prevail on the fact that neuro effect can be by direct conquest or by adaptive provocative comeback. The patients with the infection should be assessed prior for neurological signs like hemicrania, skin crawling, consciousness disorders. In time evaluation of cerebrospinal fluid will help in being pre-prepared for the worst-case scenario of complications and will help cure them.

With the alarming number of infections, the chances of virus entering the brain increases in severe cases. One should be alert of all the probabilities of catching the virus and thus neuro disorder. The studies should continue to explore the underneath process and the part of neurological impact. Therefore, it is very important to break the chain of transmission before it breaks us.

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