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Neurological dysfunction in Covid infection a review article

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ABSTRACT: In December 2019 the pandemic broke out as the novel coronavirus SARS-CoV-2 from Wuhan, China which has now spread into a worldwide severe life threatening contagion. Recent studies suggest that this virus is it is not just affecting the lung but also the human brain which is now emerging as the new target of the virus. The main neurological indicator of COVID-19 is loss of smell or taste (anosmia and ageusia) It may also result in encepaholopathy which is a severe disorder and one should be immediately aware to hold the situation not to get exacerbate from here. Although these neurological dysfunction were not reported by most of the early studies from China but later on high prevalence of anosmia and ageusia were reported in European COVID-19 patients. To counteract the epidemic, Researchers need to frame more precise therapeutic stratagems with the available information. In this Perspective, we tried to provide a brief outline of the presently known neurological indices of COVID-19 and a detailed description of the most common indication in the present time, of anosmia and ageusia deliberate some possible means to design therapeutic approaches to overcome the present world wide disaster.

I. INTRODUCTION:

Coronaviruses (Cov) have instigated noxious outbursts in the past too. In China in 2002-2003 the first pandemic was caused by Severe acute respiratory syndrome coronavirus (SARS-CoV), affecting more than 8000 people, with a mortality rate of 10% while another outbreak of Cov was reported in 2012 from Saudi Arabia, the Middle-East Respiratory Syndrome coronavirus (MERSCov) affected around 2500 persons with a mortality rate of 35% and now in December 2019, novel Corona Virus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initiated in Wuhan, China, (1) The COVID-19 is affecting 215 countries and territories around the world. To date, over 40 million cases of confirmed COVID-19 have been reported worldwide,

The novel SARS-CoV-2 and initial SARS-CoV both are almost identical taxonomically. With genetic similarity of 70-80%.Coronaviruses, are named after their crown-like appearance on electron microscopy having a diameter of approximately 100 nm, They are single stranded ribonucleic acid (+ss-RNA) viruses. SARS-CoV-2 comprises of unique sequences, having a polybasic cleavage site in the spike protein, which is a potential element of augmented transmissibility. (2).The spike protein of SARS-CoV-2 binds to its cellular receptor, the angiotensin converting enzyme 2 (ACE2), on mammalian host cell. ACE2 also acts as receptor for SARS-CoV. Viral entry occurs after proteolytic cleavage of the spike protein by the transmembrane protease.It is widely accepted that SARS-CoV-2infectivity and entry into the body depends on its binding to the ACE2 host receptor.ACE2 is expressed abundantly in lung alveolar cells, but also in many cell types and organs in the body, including the cerebral cortex, digestive tract, kidney, gallbladder, testis and adrenal gland.(3)ACE 2 receptors are also found in glial cells in brain and spinal neurons. Hence it can attach, multiply and damage the neuronal tissue.

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Though as the name itself suggests that these viruses are identified exclusively as severe acute respiratory syndrome coronavirus but the previous studies on SARS-CoV patients has proved that the coronaviruses affect the brain too.

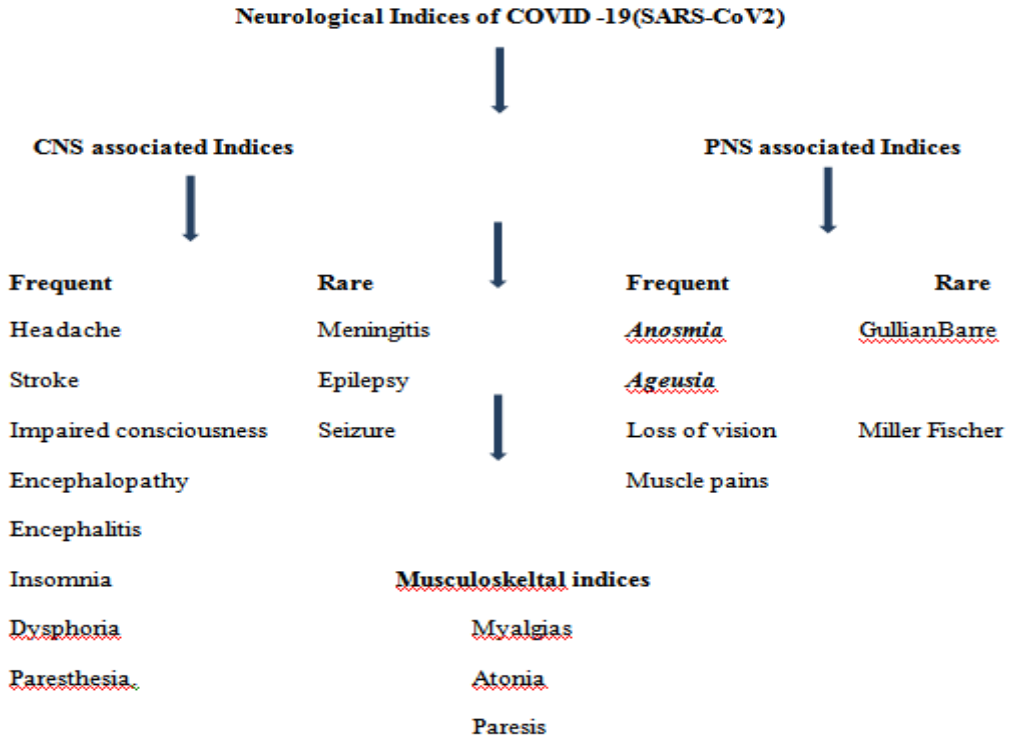
It has been reported that in addition to conventional respiratory and cardiovascular complains, several patients of COVID-19 also exhibit common neurological symptoms like Anosmia, Ageusia, headache, dizziness, and neuralgia while rare complications including encephalopathy, acute cerebrovascular diseases, impaired consciousness and skeletal muscular injury were also reported[4,5]. The present review is aimed to analyze the neurological index of COVID-19 with main focus on themost common neurologic complaints in COVID-19 like anosmia andageusia. Other reported diseases, such as headache stroke, impairment of consciousness, seizure, and encephalopathy will also be explained briefly.

SARS-CoV-2 virus like its other family members, first infect the peripheral nervous system and then enters the CNS either through the synapse-connected route or olfactory system (6) The possible entry point are the ACE2 receptors present on endothelial cells of cerebral vessel. Previous studies on transgenic mice perceived that when the SARS-CoV and MERS-CoV viruses were administered intranasally they infiltrate the brains.(7) This infiltration of the viruses into the brain took place through the olfactory nerves, ultimately affecting the thalamus and the brain stem. The brain stem was finally found to be the worst infected.(7) So, following these experimental studies along with the hematologic spread of SARS-CoV-2 in CNS, retrograde neuronal transport of the virus through the vagal nerve afferents from the lungs into the CNS must be taken into consideration.(6) Also, with reports claiming infection of the gastrointestinal tract by SARS-CoV-2,the virus could even use the enteric nervous system and its sympathetic afferent neurons to reach the CNS.(6)

As the central, peripheral and Musculoskeltal nervous system, all can be affected in COVID- 19 the neurological manifestation were classified into 3 categories

1. The CentralNervous System (CNS) associated manifestation
2. Peripheral NervousSystem (PNS) associated manifestation.
3. Musculoskeltalassociated manifestation

Neurological Indices of COVID -19(SARS-CoV2)



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Frequent Indices:

Headache is the most frequent neurological symptomsin patients with COVID-19. (8, 9). In a case series,(10) headache was a major complaint, besides fever, cough, sore throat, and breathlessness. Interestingly, headache can occur even in the absence of fever and can be exhibited as a migraine, due to tension, or cluster headache (11).Pervasiveness of headache varies in different reports but can affect up to one-third of diagnosed patients.(12,13) While headache is a well-described indicator of encephalitis, meningitis, vasculitis, and intracranial hypertension, Exact pathophysiological connection of headache with COVID-19remained unexplained, the possible reason might be increased mental stress, excessive anxiety, and changes in lifestyle.(14). There is no specific treatment alternatives for COVID-19-related headache were reported hence a vigilant pain management is endorsed.

Stroke is another very common index of Covid 19 and the risk factor measured for this might be infection. Several studies showed the probability of increased prevalence of stroke all through the weeks following a COVID-19 may perhaps is reported in otherwise low risk patients [15]. These studies propose that stroke has a significant prevalence in COVID-19 and treatment of stroke can be comparable to as in COVID-19 distinct cases [16]. Another study by Mao et al. (17) found that in 3% of patients with COVID-19 revealed stroke as their only neurological indices of the disease.

Encephalopathy: Impaired consciousness, presenting with confusion, lethargy, delirium, or coma in Covid 19 patients are charactersic of encephalopathy .(18) which is a kind of reversible brain dysfunction syndrome caused by factors like systemic inflammatory response syndrome– associated toxemia and hypoxia throughout the procedure of acute pulmonary infection.(19) Earlier Mao et al in their cohort study observed headache and encephalopathy in 40% of patients but they have not described the details and the diagnostic criteria used in their observation [20)Later on in a retrospective study of the clinical characteristics from China, Chen et al. presented the data of 113 COVID-19 patients and recognized hypoxic encephalopathy in only 20 patients [21]. The frequency of encephalopathy was significantly lesser in the patients who had recovered.

Elder individuals particularly those presented with prior reported chronic medical conditions are at an increased risk of Delerium or impaired consciousness in the situation of acute infections, these patients which are prone to experience COVID-19 severely, may present with confusion and encephalopathy [22].

Acute necrotizing encephalopathy (ANE) is an infrequent progressive neurodegenerative disorder characterized by multiple, symmetric areas of edema and necrosis in the CNS, which has been related to the intracranial cytokine storms which result in blood-brain-barrier breakdown during a febrile disease such as influenza [23,24].; and the latest data suggests that a subgroup of patients with severe COVID-19 might have cytokine storm syndrome and brain lesions that may include the thalamus, brainstem, cerebral white matter, and cerebellum Neurological manifestations of COVID-19/ANE leads to disruption of BBB without direct viral invasion

Encephalitis is very common cause of morbidity and mortality due to severe complications of different viral infections. Covid 19 is also associated with these neurological manifestation in humans. United States and China in three additional cases has concluded the occurrence of encephalitis as the initial and even only indices of COVID-19 (25-27).

Insomnia /Dysphoria /Paresthesia are another frequent neurological manifestation of Covid 19.

PNS ASSOCIATED INDICES

PNS associated indices of COVID-19 are not as severe as CNS indices and these incudes anosmia, ageusia / hypgeusia, loss of vision, pain in muscle, Guillain-Barre syndrome (GBS) and Miller Fischer syndrome(MFS [28]:

Frequent Indices

Anosmia:

Anosmia is one of the most frequent PNS associated indices of Covid 19 (SARS-COV-2), and it is also reported in prior coronaviruses. Smell loss is an olfactory disorder and is associated to an ample array of viral infections**.[**29, 30] Due to viral injure of the olfactory epithelium, infection of the upper respiratory tract occurs which can cause acute-onset of anosmia.**[**30) along with other olfactory disorders like extreme nasal secretion or nasal obstruction These symptoms occur all of a sudden [31]. However, some authors consider that anosmia is someway due to inflammation in the olfactory nerves which may hinder the sense of smell rather than damage to the structure of the receptors [32]. Although, relevance of nasal corticosteroids is not recommended due to the uncertainty of their benefits [33].

Anosmia is detected in the begining of SARS-COV-2 infection and it can be elucidated

by injure to the olfactory nerve throughout invasion and multiplication of this virus. thus, anosmia may be more frequently observed in the COVID-19 patients than other respiratory viral infections. It is now clinically apparent that inception of smell disorder was significantly more common among COVID-19 patients (39%) than influenza patients (13%). They generally had an severe onset and was commonly an initial indices. Associated nasal obstruction was uncommon in COVID-19 patients.(34)

Anosmia is generally present as the initial appearance of the disease in asymptomatic persons with no additional symptoms [35]. Hence, it was suggested by some researchers that populace having these symptoms should isolate themselves from others as they may be potential carriers of the disease. The majority of patients steadily recoup their sense of smell and taste as soon as they convalesce from the infection of SARS-COV-2 [33]. Though, numerous hypotheses are anticipated for elucidation of anosmia, Yet the precise mechanisms related with SARS-COV-2 anosmia are not still clear. A study in animal models proposed that through olfactory pathways coronavirus can transneuronally disseminate into the brain and through the expression of the gene TMPRSS2 and ACE2 in sustentacular cells it invade the olfactory neuroepithelium integrity [36, 37]. Therefore, injure to the olfactory receptors may be arbitrated in some way through SARS-CoV-2 uptake into other cells decisive for supporting the olfactory receptor cell population. For instance, olfactory ensheathing glial cells that encircle the olfactory receptor cell axons and shape the olfactory fila are one contender by which ACE2-independent virus transfer can occur into olfactory receptor neurons by means of exosomes. A probable scenario recommend that at this point olfactory receptor neurons may instigate a rapid immune response in the host with the manifestation of olfactory dysfunction.(38) Therefore, as a result of disruption of olfactory neuroepithelium anosmia arises. Damage to the olfactory nerve during invasion and multiplication of SARS-CoV-2 possibly will elucidate anosmia observed in the early phase of COVID-19. Thus, anosmia or ageusia may be more often observed in the COVID-19 patients than any other respiratory viral infections.

As aforesaid, Anosmia is now established as an indicative clinical symptom for COVID-19 infection [39]. Till date, it remains still contentious where precisely Anosmia stands in COVID-19 clinical picture in terms of severity. Anosmia can appear earlier than the respiratory symptoms of COVID-19, since the inception of these symptoms preceded distinctive symptomatology.

Inflammation in the nasal cavity may obstruct the sense of smell, may be due to the virus that infects and damages cells in the nasal epithelium. Conventional psychopathologist has illustrated the occurrence of anosmia as an "atmospheric," non-expressed sensorial experience which goes ahead of the objective measures but that can however be felt subjectively. As these atmospheres have much to do with smell and flavor, our capability to perceive an atmosphere is the ability to "smell an atmosphere": smell and flavour generate numerous and imperceptible frontiers that, selectively and affectively, pass through the complete human world. Therefore, olfaction plays a major role in emotional processing, reminiscence, and communal behaviors [40], The association between perception and movement proves enduring; smelling is at all times also breathing, as tasting is always swallowing or chewing [41].

Preliminary studies illustrated that patients presented with anosmia have less severe symptoms and they seem to be younger [42]. On the other hand, it seems that among hospitalised patients fewer have olfactory dysfunction [43]. Mao et al. in their study found that out of 214 hospitalised patients only 5% complained anosomia with a mean age of 52.7 [17]. This suggests that anosmia could turn out to be a optimistic prognostic factor, supporting the notion that anosmia could reflect an efficient defence approach against the virus. Furthermore, it can not be predicted at the moment that COVID-19-related anosmia or its absence may also be associated to long-term neurological disease

For the perception of the precise mechanism fundamentals behind COVID-19-related olfactory manifestation further molecular experiments on animal models will be required. However, although the majority of biological pathways may be very similar amongst mammals, olfaction, in terms of impact on survival is much more significant for mice than humans. This means that to entirely investigate the interactions between coronavirus neuroinvasion, apoptosis, immune reaction and neurogenesis, further research will have to be performed on fresh human olfactory mucosa sample. This can be done by excision of a segment of the olfactory cleft as part of a transnasal endoscopic surgery performed for an unrelated rhinological condition(44)

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Ageusia

The complaint of taste loss (Ageusia) by a significant number of COVID-19 patients most likely reveal, to a considerable degree, injure to the olfactory system, rather than damage to the taste buds hence Ageusia is considered to be a secondary consequence of olfactory dysfunction. However, the ACE2 receptor, the main host cell receptor of SARS-CoV-2 which binds and penetrates cells, is generally expressed on epithelial cells of the oral mucosa(45). Damage of mucosal epithelial cells of the oral cavity may explain ageusia observed in the early stage of COVID-19. This evidence may explain the pathogenetic mechanism underlying ageusia in COVID-19.(46)

Thus, the vast majority of individuals who clinically present with complaints of taste loss actually exhibit smell dysfunction, including those with a viral etiology.(47) Taste bud-mediated sensations are largely limited to the vital taste qualities of sweet, sour, salty, bitter and savory , With the exception of such sensations, all "tastes" are flavor sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.(48) This tendency for many persons with smell loss to misconstrue their problem as taste loss (47) must be considered in studies relying only on self-report. Potential research employing quantitative taste tests is evidently required to definitively ascertain whether SARS-CoV-2 also can damage taste buds or, in exceptional cases, more central brain regions related to taste.

Guillain barre syndrome (GBS)

The first case of a 61 year old female with COVID-19- related GBS was reported from Wuhan, China on Jan 23, 2020. The patient was presented with progressive bilateral weakness in her lower extremities and severe fatigue, progressing within 1 day [49]. She made a good motor recovery after isolation and administration of anti-virals. Later Toscano et al published the data of five patients presented with GBS from Northern Italy [50]. The main presenting features in 4 patients who had positive PCR for Covid 19 from the nasopharyngeal swab on initial visit were lower-limb weakness and paresthesia, while facial weakness, ataxia, and paresthesia in one patient who was initially negative but later turned positive. These patients were treated with IVIG which was repeated in 02 patients while one patient had plasma exchange. After one week, only one patient was capable to ambulate independently and discharged from the hospital. The author concluded that to prove the fundamental relationship between COVID-19 and GBS, large scale studies are required.

II. CONCLUSION

The predictive assessment and biomarkers of the SARS-CoV-2 and its effects on the CNS and PNS differ among patients depending on age, severity of the disease, immunocompetency and comorbidities. Opportune management of the symptoms can increase the rate of survival and have a constructive prognosis which will decrease the long term effects

The incidence of neurological manifestation in COVID-19 patients include CNS associated indices like headache, dizziness, encephalopathy, encephalitis and PNS associated indices like Anosomia, Ageusia, , GBS etc These manifestation can affect the quality of life due to its devastating nature as well as carries a considerable risk for mortality.

Anosmia and ageusia in particular seem to be part of important symptoms and indication of the disease in the early stage which helps in the diagnosis of COVID-19. The severe anosmia or ageusia required to be documented as vital symptoms in patients with asymptomatic-to-mild disease severity.

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