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Immune mediating molecules and pathogenesis of COVID-19-associated neurological disease

HariOm Singh [a,*], Amita Singh [b], Abdul Arif Khan [c], Vivek Gupta [d]

[a] Department of Molecular Biology, ICMR-National AIDS Research Institute, Pune, India
[b] District Women Hospital, Prayagraj, UP, 211003, India
[c] Department of Microbiology, ICMR-National AIDS Research Institute, Pune, India
[d] Department of Biochemistry, ICMR-National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, 282001, India

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ABSTRACT

Background: Long period of SARS-CoV-2 infection has been associated with psychiatric and cognitive disorders in adolescents and children. SARS-CoV-2 remains dormant in the CNS leading to neurological complications. The wide expression of *ACE2* in the brain raises concern for its involvement in SARS-CoV-2 infection. Though, the mechanistic insights about blood-brain barriers (BBB) crossing by SARS-CoV-2 and further brain infection are still not clear. Moreover, the mechanism behind dormant SARS-CoV-2 infections leading to chronic neurological disorders needs to be unveiled. There is an urgent need to find out the risk factor involved in COVID-19-associated neurological disease. Therefore, the role of immune-associated genes in the pathogenesis of COVID-19 associated neurological diseases is presented which could contribute to finding associated genetic risk factors.
Method: The search utilizing multiple databases, specifically, EMBASE, PubMed (Medline), and Google Scholar was performed. Moreover, the literature survey on the involvement of COVID-19, neuropathogenesis, and its consequences was done.
Description: Persistent inflammatory stimuli may promote the progression of neurodegenerative diseases. An increased expression level of cytokine, chemokine, and decreased expression level of immune cells has been associated with the COVID-19 patient. Cytokine storm was observed in severe COVID-19 patients. The nature of SARS-CoV-2 infection can be neuroinflammatory. Genes of immune response could be associated with neurodegenerative diseases.
Conclusion: The present review will provide a useful framework and help in understanding COVID-19-associated neuropathogenesis. Experimental studies on immune-associated genes in COVID-19 patients with neurological manifestations could be helpful to establish its neuropathogenesis.

1. Introduction

SARS-CoV-2 associated neurological complication is an emerging issue [1]. It is associated with the "intracranial cytokine storm" which is an acute hyperinflammatory condition leading to the severity of several viral infections [1]. The "intracranial cytokine storm" commences with the aberrantly enhanced immune cells activities resulting in blood-brain barrier breakdown and involves symmetric, multi-focal lesions. The occurrence of SARS-CoV-2 associated central nervous system (CNS) complications is ~0·04% [2]. The severe and critical COVID-19 patients have a higher chance of SARS-CoV-2 associated neurological complications [3,4]. The viral infiltration in the brainstem increases the chance of CNS pathology [5]. The psychiatric and cognitive disorders in adolescents and children can be developed after a long period of SARS-CoV-2 infection. Genes of immune response play a major function in antiviral immunity, such as cytokines and chemokines involved in the activation of immune cells through the generation of granulocyte-macrophage colony-stimulating factor (GM-CSF) activate the inflammatory process.

SARS-CoV-2 susceptibility and its clinical outcome are influenced by the expression of cytokines and chemokines and other immune regulating genes and the function of these proteins. These factors are associated with the change in synaptic pruning during childhood, adolescence, and adulthood. The dormant persistence of SARS-CoV-2

* Corresponding author. Department of Molecular Biology 73 'G' Block, MIDC, Bhosari, NARI, Pune, 411026, India.
E-mail addresses: hariomsgpgims@gmail.com, hsingh@nariindia.org (H. Singh).

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infection may increase the secretion of inflammatory proteins which can stimulate the development of neurodegenerative diseases.

Following the infection of SARS-CoV-2, the release of cytokines like IL-1 and IL-6 from local tissue may trigger several neuropathogenic phenotypes, such as dementia, cognitive and movement disorders and epileptic seizures [6–8]. However, till now there is no direct evidence of this hypothesis.

ACE2 is present in various organs including skeletal muscles and the nervous system [9]. It is expressed in the endothelial cells of the brain. The SARS-CoV-2 uses ACE2 receptor for cellular entry where S1 protein attaches and binds with ACE2 of endothelial cells and directs viral infection in the brain. Therefore, it may contribute to neurovascular damage among COVID-19 patients [10]. Since *ACE2* is expressed in the various brain compartments and binds with the S1 protein, it is involved in SARS-CoV-2 infection through several indirect or direct mechanisms. So far, evidence for SARS-CoV-2 associated CNS complication has not been well documented, however, the SARS-CoV-2 genome isolated from the CSF of COVID-19 patients suggests direct viral neuroinvasion [11].

SARS-CoV-2 infection is associated with disturbances in taste perception and smell, including anosmia [12–17]. In COVID-related anosmia, SARS-CoV-2 persuade transient changes in odour perception due to inflammatory responses [16,18,19]. It often recovers over weeks [16,20,21], but recovery from typical post-viral anosmia often takes months because of direct damage to olfactory sensory neurons (OSNs) [22–24]. This suggests that SARS-CoV-2 may target odour processing by a certain unidentified mechanism different from those used by other viruses.

So far, the range of COVID-19 associated neurologic manifestations has not fully demonstrated [25]. Besides, how SARS-CoV-2 cross the blood-brain barriers (BBB) and infect microglia and astrocytes is still not fully understood [26]. Therefore, the text was compiled to correlate the immune-associated genes with SARS-CoV-2 associated neurological pathogenesis including SARS-CoV-2 entry into the brain cells.

2. Method

The search utilizing multiple databases, specifically, EMBASE, PubMed (Medline), and Google Scholar was performed. Moreover, the literature survey on the involvement of COVID-19, neuropathogenesis, and its consequences was done.

2.1. CNS cells expressing ACE2 and COVID-19-associated neurological disease

ACE2 is expressed in oligodendrocytes, astrocytes, neurons, and monocytes/macrophages [27,28]. It is also expressed in dendritic cells and macrophage, assisting pulmonary invasion by SARS-CoV2, and induces the local and systemic uncontrolled inflammatory responses [29, 30]. Host cell protease, Furin and *TMPRSS2* are also expressed in macrophages and have a role in SARS virus binding and fusion of the membranes [31], similar to ADAM 17 acting as sheddase of ACE2 [32]. Thus, the virus enters into dendritic cells and macrophages where it replicates in the presence of all these components and activates the abnormal production of proinflammatory chemokines and cytokines [33]. Immediately, after the SARS-CoV-2 infection in macrophages, it increases the expression of proinflammatory chemokines. On the other hand, it reduces the production of antiviral cytokines [34]. The study showed that dendritic cells are susceptible to SARS-CoV2 infection but are not able to support viral replication [35].

Following SARS-CoV-2 infection, S1 protein binds with *ACE2* expressed in neuron, glial and capillary endothelium cells, olfactory bulb pericytes and dorsally-located olfactory epithelial cells leading to anosmia and related disturbances. Besides, S1 protein binds with *ACE2* expressed in the olfactory neuroepithelium and cribriform plate of the ethmoid bone leading to its CNS entry and subsequent neuronal death (Fig. 1a and 1b). In the CNS, SARS-CoV-2 gains entry via olfactory bulb and reaches into the brainstem where it causes cytopathy and death of neurons. Thus, SARS-CoV-2 may contribute to the development of COVID-19-associated neurological complications.

2.2. Association of neuronal and immune cells with COVID-19-associated CNS injury

Following the infection of SARS-CoV-2, S1-protein binds with the *ACE2* expressing neurons, glial cells, dendritic cells, monocytes, macrophages. Subsequently, the virus activates these cells to get infiltration of other immune cell subsets and replicate. It results in abnormal production of proinflammatory proteins by these cells. On the other hand, it

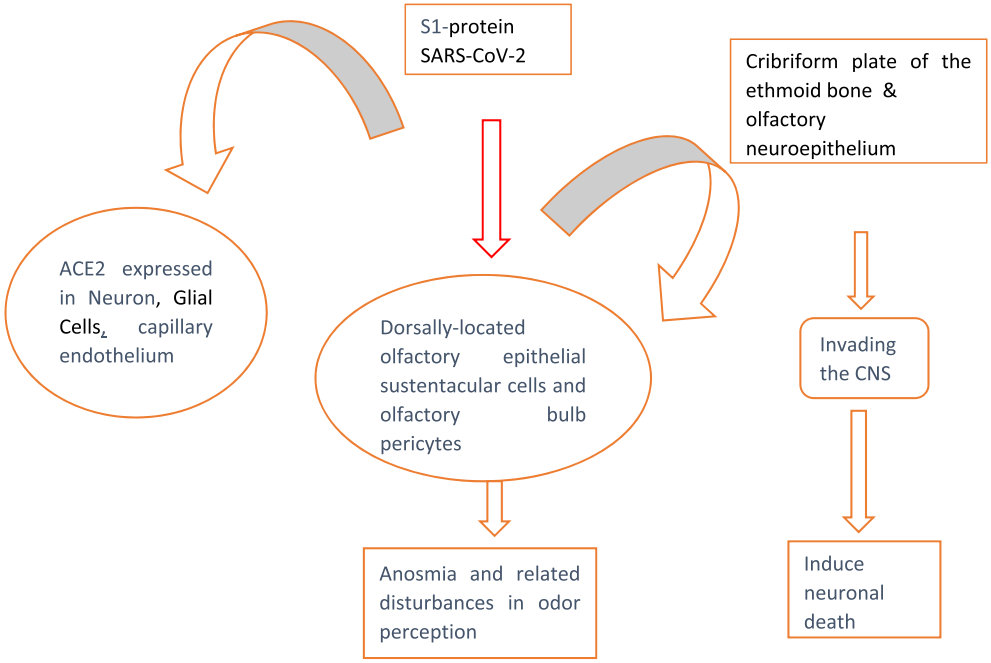

Fig. 1a. ACE2 expression in CNS cells and COVID-**19-associated neurological disease**.

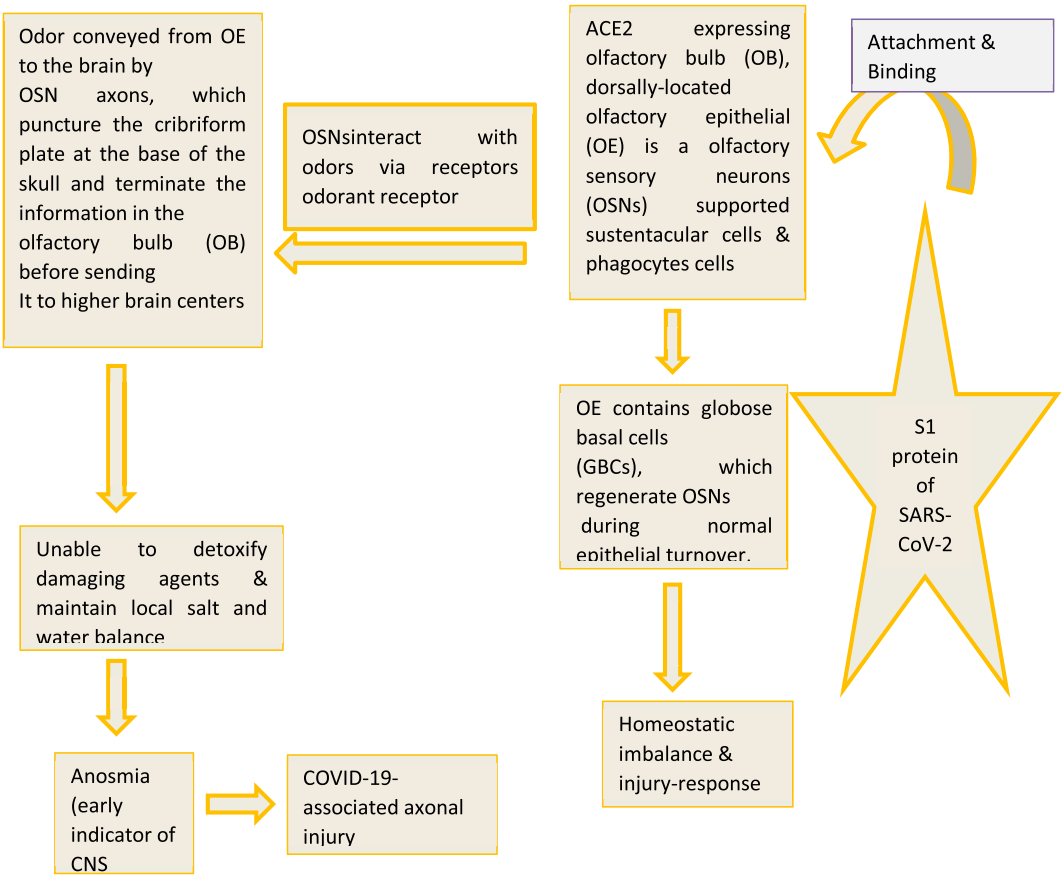

Fig. 1b. Epithelial cells and COVID-19-associated axonal injury.

reduces the production of antiviral cytokine. This leads to the induction of local and systemic inflammatory responses in the CNS developing COVID-19-associated CNS injury (Fig. 2).

Innate immune systems have an important role in the response towards external stimuli. An aberrant immune system results in excessive dysregulation of the innate immune response. The defective regulation of immune cells (CD4 and CD8 T cells, CD3, NK cells, CD16, CD56 cells) and continuously increased production of inflammatory proteins (cytokine storm) are associated with the severity of COVID-19 disease [36]. Cytokines (IL-1β, IFN-γ, IL-12, IL-33, IL-6, IL-18, IFN-α), transforming growth factor (TGF-β) and chemokines (CCL2, CCL3, CCL5, CXCL9, CXCL10) are inflammatory mediators, released by immune effector cells [37].

SARS-CoV-2 infection induces increased production of inflammatory proteins which generates an abnormal immune response and modifies the function of immune cells. The persistent abnormal immune response allows the viral infiltration in the brainstem that may contribute to the development of COVID-19-associated neurological complications. Sometimes, individuals may experience neurological complications because of a post-COVID-19 mediated deregulated immune response that can continue as persistent inflammation, immunosuppression, catabolism syndrome (PICS).

2.3. Association of immune-associated genes and COVID-19-associated neurological disease

During SARS-CoV-2 infection, S1 protein binds with *ACE2* expressed in neuronal cells (glial cells and neurons), immune cells (macrophages, monocytes, and dendritic cells) resulting in reduced production of antiviral cytokine in brain cells. It increases the secretion of proinflammatory chemokines and cytokines in the CSF. On the other hand, it decreases the expression level of immune-responsive genes leading to dysregulated immune response. Following immune-associated genes contribute to the development of COVID-19-associated neurological complications (Fig. 3).

2.4. Indoleamine-2, 3-dioxygenase 1 (IDO1)

IDO1 (8p11.21) is known as a suppressor of inflammation. Failure of balance between inflammatory response and IDO1-mediated tolerance leads to inflammation and subsequent susceptibility to infection due to decreased immunity against the pathogen. *IDO* gene is expressed in macrophages, monocytes, dendritic cells, microglia, and several other immune cells and influences neurological complications [38]. *IDO* is induced by viruses and IFN-inducers, such as lipopolysaccharide (LPS) [39]. SARS-CoV-2 S1 protein binds with *ACE2* expressed in dendritic cells, monocytes, macrophages resulting in aberrant IDO1-mediated tolerance and inflammatory response. Therefore, the *IDO1* gene may contribute to developing COVID-19-associated neurological complications.

2.5. Nitric oxide (NO) synthase or inducible nitric oxide synthase (iNOS or NOS2)

NOS2 (17q11.2) is present in the glial cells. NOS and NOS2 are inflammatory mediators, with immunopathological and protective capabilities [40]. NOS2 is involved in the production of NO during inflammatory states, and plays an important role during allergic diseases including bronchial asthma [41,42]. Binding of S1 protein with *ACE2* expressed in the glial cells interrupts NOS2 mediated protection which

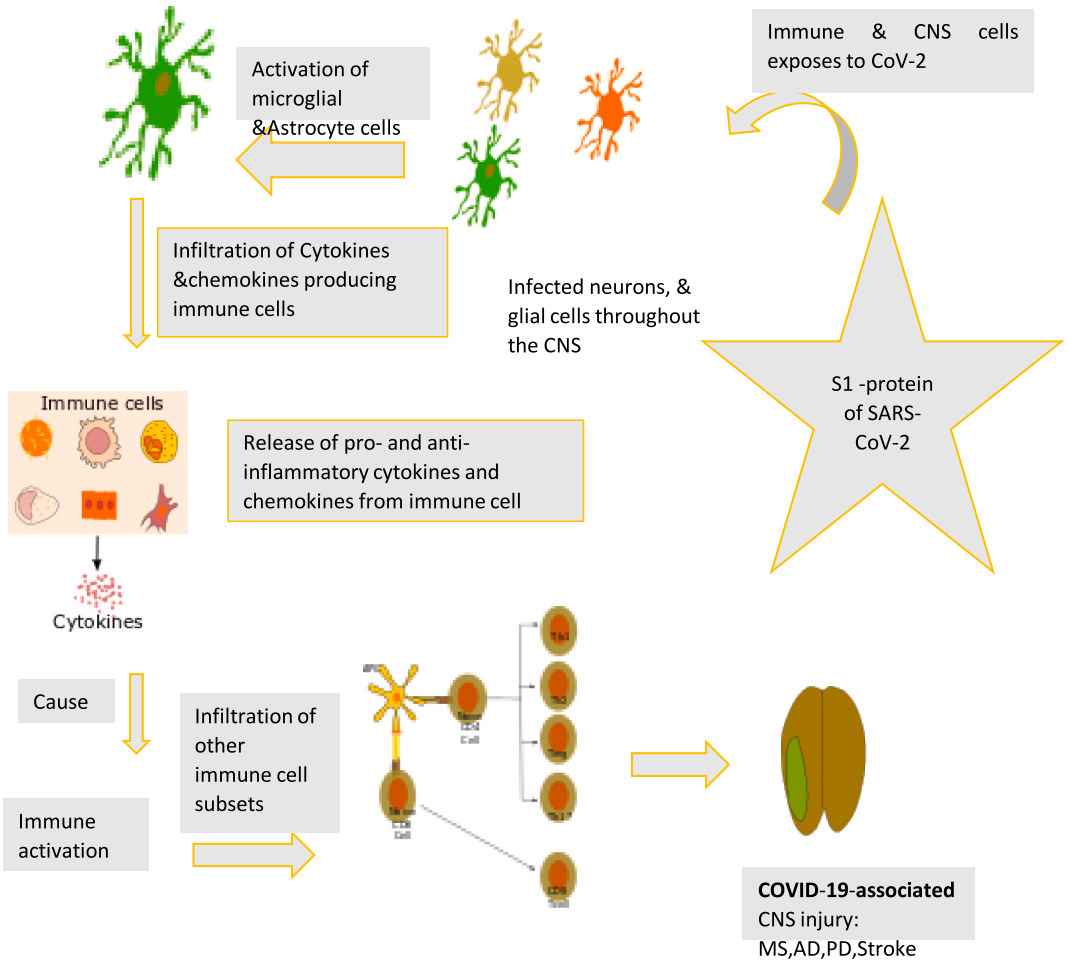

Fig. 2. Association of neuronal and immune cells with COVID-19-associated CNS Injury.

abrogates immune homeostasis. These attributes of the *NOS2* gene provide several caveats for its contribution to COVID-19-associated neurological complications.

2.6. 2′, 5′-Oligoadenylate synthetase 1 (OAS1)

OAS1 (2q24.13) is induced by type I interferon and has a role in host defense against viral infections [43]. It is expressed in neurons, astrocytes, and oligodendrocytes [44] and converts ATP to 2′,5′-oligoadenylates (2–5As) in presence of dsRNA or ssRNA. Production of 2–5As activates latent RNase L which degrades single-stranded RNAs and inhibits viral replication [43]. Single nucleotide polymorphisms (SNPs) of the *OAS1* gene are known to modulate its expression level and enzyme activity resulting in modulated susceptibility and severity of viral diseases [45]. During S1 protein binding with *ACE2* expressed in neurons, astrocytes, and oligodendrocytes, OAS1 mediated host defense against infections gets interrupted leading to abrogated immune response. It further supports the contribution of the OAS1 gene in the development of COVID-19-associated neurological complications.

2.7. Human leukocyte antigen (HLA)

HLA [6p21] gene is widely known for its major contribution to the immune response against foreign antigens including viruses [46]. Macrophages or microglia express the histocompatibility glycoprotein (HLA-DR) which is involved in several neurological diseases, such as Pick's and Huntington diseases, Parkinson, Alzheimer, Shy-Drager syndrome, amyotrophic lateral sclerosis, multiple sclerosis, AIDS encephalopathy, and parkinsonism-dementia of Guam [47]. HLA-DR has a role in immune response and facilitates immune surveillance by eliminating foreign antigens. HLA-DR has been mapped to assess the susceptibility or protection in numerous neurological diseases, like neuromyelitis optica, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson, Alzheimer, myasthenia, schizophrenia, and gravis [48]. HLA may increase the binding specificity between the ACE2 receptor and S protein and increases the progression of COVID-19. Several HLA types are associated with the occurrence of SARS infection [49], for instance, the *HLA*-B*4601 allele is involved in the severity of COVID-19 in Asian populations [49]. Moreover, individuals with *HLA*-A3.1 allele are susceptible to SARS coronavirus [49]. The ratio of Cw*0801 homozygous and heterozygous alleles was 4.4:1 among individuals with SARS-CoV infection. In contrast, individuals having *DRB1*0301* and *HLA*-Cw*1502 alleles may serve as resistance factors for SARS infection [50]. Also, *HLA*-B*4601 alleles were significantly correlated with the severity of SARS in the Taiwan population [51]. The frequency of the *HLA*-B*4601 allele was higher among the suspected SARS infected individuals, and is further increased significantly among the severe patient group [52]. There was a significant association between the *HLA*-B*0703 allele and SARS development in the Chinese population [53]. Some of the *HLA*-C variants may trigger neuroinflammation through the release and accumulation of $\beta_2$microglobulin (β_2m) during viral infections.

Interaction of viral S1 with *ACE2* expressed on microglia or macrophage cells leads to the interruption of HLA-DR mediated host defense against infections. The major role of HLA-DR in immune response further indicates its contribution towards the development of COVID-19-

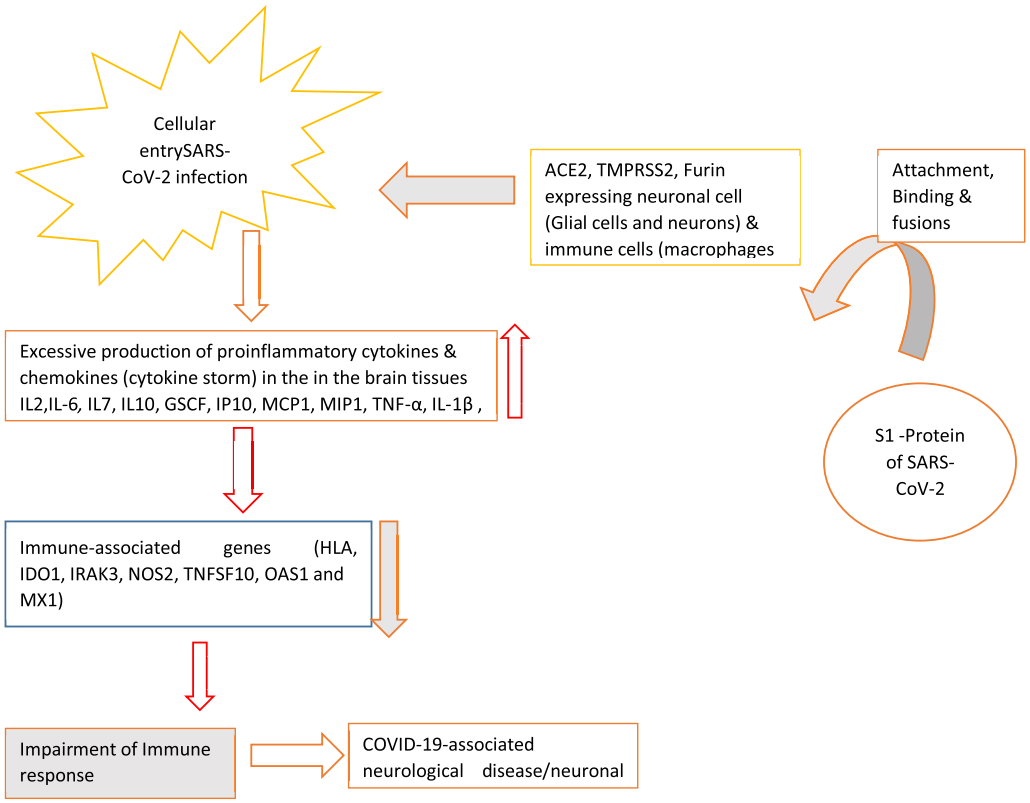

Fig. 3. Immune-associated genes and COVID-19-associated neurological disease.

associated neurological complication.

2.8. Tumor necrosis factor-β (TNFSF1)

TNFSF1 (6p21.3) controls the expression of inflammatory cytokines and the progression of inflammation. TNF-α is produced from astrocytes, microglia, and neurons [54] and it is highly expressed in several clinical conditions, such as spinal cord injury [55], stroke [56], and sciatic nerve injury [57]. TNF-α expression stimulates inflammation and neuronal cell death. Elevated TNFα level is associated with severe COVID-19 patients [58]. *TNFα* −1031CT/CC and −863 AC genotypes may have risk factors for discharged SARS patients [59]. *ACE2* is expressed in oligodendrocytes, neurons, astrocytes, and glial cells (astrocytes and microglia) [27]. During SARS-CoV-2 infection, TNF-mediated immune cell regulation gets disrupted leading to the abrogated immune response and indicates the potential of TNF in the development of COVID-19-related neurological complications.

2.9. Inflammatory cytokine genes and pathogenesis of COVID-19-associated neurological complications

2.9.1. Interleukin-2 (IL-2)

IL-2 (4q27) is known as an inflammatory cytokine with both pro and anti-inflammatory activity. It is involved in the regulation of the immune system and the pathogenesis of asthma. IL-2 or IL-2R molecules are found in the cerebellum, hippocampal formation, septum, frontal cortex, hypothalamus and pituitary fibre tracts such as the corpus callosum striatum, and locus coeruleus. *ACE2* and *IL-2R* are expressed in both neuronal and glial cells. IL-2R (IL-2R alpha) serves as receptor for IL-2.Further, after binding of IL-2 with its receptor (IL-2R alpha), IL-2 penetrates the BBB and controls the communications between the CNS and peripheral tissues. The functional and pathological changes in the brain are affected by communication between IL-2/IL-2R. Enhanced serum IL-2 level was associated with severe COVID-19 patients [58]. As mentioned above the involvement of IL-2 in SARS-CoV-2 infection indicates its contribution to the development of COVID-19-related neurological complications.

2.9.2. Interleukin 10 (IL-10)

IL-10 (1q32.1) is an immunosuppressive cytokine produced within the CNS and acts as an anti-inflammatory factor. *IL-10* regulates inflammatory response to infections under various conditions including, glial inflammatory responses, CNS catheter infection, and peripheral inflammation [60,61]. Clinical evidence indicated association of elevated IL-10 level with ICU admitted COVID-19 patients [59]. It is suggested in the literature that, *IL-10* -1082G/A and −592A/C polymorphism could be associated with SARS infection [62]. As *ACE2* is highly expressed in neurons and glial cells, CNS could be a potential target for SARS-CoV-2 [63] and IL-10 can play a major role in this process through regulation of inflammatory response.

2.9.3. Interleukin 6 (IL-6)

IL-6 (7p15.3) is an inflammatory cytokine implicated in both pro and anti-inflammatory activities and has an important role in response to acute lung injury. A higher plasma IL-6 level was correlated with the risk of severe respiratory failure in COVID-19 patients [64]. Another study indicated increased levels of IL-6, and ACE in CSF of SARS-CoV-2–associated encephalitis patients [65]. Clinical studies indicated that *IL-6* 174G/C polymorphism influences IL-6 levels and higher plasma IL-6 levels are associated with severe COVID-19 among the study group [66]. *IL-6* polymorphism is suggested to be used as an indicator of severity in COVID-19 patients in the Korean population [67]. IL-6 depends on GM-CSF and JAK2 signaling and SARS-CoV-2 can play an important role in this process. Hence IL-6 could be a potential therapeutic target for hyperinflammatory response [68]. In COVID-19 patients, IL-6 could be important for fibrogenesis and endothelial cell dysfunction [67]. IL-6 is produced by both astrocytes and microglia [68] and its neuronal expression contributes to the glial cell activation [69].

ACE2 is also expressed in neurons, astrocytes, and glial cells [27,70], and therefore the S1-ACE2 interaction can be affected through IL-6 contributing to the development of COVID-19-associated neurological complications. Moreover, the inhibitors of IL-6 are suggested to reduce the COVID-19 associated mortality without increasing secondary infections [71].

2.9.4. Interleukin 7 (IL-7)

IL-7 (8q21.13) is an inflammatory cytokine involved in lymphoid cell survival and maintenance of naive and memory T cells. The study indicated the presence of IL-7 in the CSF and its high level is associated with inflammatory CNS disease [72]. Increased *IL*-7 mRNA expression was detected in the CNS [73] and elevated serum IL-7 levels, along with other circulating cytokines and chemokines is associated with the severity of COVID-19 disease [58]. *ACE2* is widely expressed throughout the CNS indicating the possible influence of IL-7 on S1-ACE2 mediated interaction and subsequent SARS-CoV-2 infection [62]. Therefore, disruption of IL-7 mediated maintenance of T cells and immune function may contribute to COVID-19-associated neurological complications and needs further investigations.

2.9.5. Interleukin 15 (IL-15)

IL-15(4q31) cytokine is involved in defense against infections including antiviral response and protection against allograft rejection and autoimmune diseases. SARS-CoV-2 induces IL-15 cytokine [74] and the viral clearance depends on several factors including, type I interferons, IL-15 and IFNγ. The clearance of SARS-CoV-2 could be inhibited by JAK1/JAK3 inhibitors, moreover, viral entry could be blocked by JAK2 inhibition [75]. IL-15 is expressed by multiple types of brain cells, including astrocytes, and neurons. Similarly, *ACE2* is also expressed in astrocytes, oligodendrocytes, and neurons [27], and it indicates the potential of IL-15 in the development of COVID-19-associated neurological complications.

2.9.6. Interleukin-1β (IL-1β)

'IL-1β (2q13) is a pro-inflammatory cytokine released by immune effector cells and play an important role as an inflammatory mediator after binding to the IL-1 receptor [36]. *IL-1* is expressed in microglia and acts as a mediator of microglial activation and proliferation. An inappropriate expression of the *IL-1* gene could lead the CNS dysfunction. IL-1 stimulates a variety of factors like adhesion molecules and endothelial cells [76] and eicosanoids [77]. The variations in these factors increase the BBB permeability and simultaneous *ACE2* expression on the neurons and glial cells leaves several caveats [70,78]. In disease condition, microglia cells are significantly activated which can contribute to neuropathology [79]. An increase in the secretion of IL-1β induces severe inflammation and therefore IL-1β gene may contribute to COVID-19-associated CNS dysfunction. In COVID-19 associated CNS disease, plasma IL-1 or CNS levels were correlated with the severities [80–85]. An increased level of *IL-1* expression and activated microglial cells can contribute to CNS pathogenesis [86]. In neuropathology and neuroinflammation, a higher *IL-1* expression was observed in the brain tissue along with morphological changes in microglia [81,87–91]. Due to the major involvement of IL-1β in several neurological conditions and its already known role in COVID-19, it needs critical investigation to evaluate its role in COVID-19 associated neurological complications.

2.9.7. Interferon-gamma (IFNγ)

IFNγ (ch12) is a pleiotropic cytokine with pathological and protective roles in CNS diseases. It is involved in Th1 responses and immunity [92] resulting in susceptibility to several inflammatory and infectious diseases. IFNγ induces proinflammatory cytokines (IL-6, IL-1, TNF-α). Individuals with *IFN-γ* +874A allele were susceptible to SARS infection in a previous report [93]. IFNγ is also expressed in neuroinflammatory and neurodegenerative conditions and provides protection during viral brain infections, however in infected neurons, IFNγ mediates a non-cytolytic viral control. *IFN-γ* and *ACE2* are expressed in the astrocytes and microglia [70,92] and therefore SARS-CoV-2 infection can affect *IFN-γ* mediated protective mechanisms in the brain. Therefore, the *IFN-γ* gene may be a potential candidate for its contribution to COVID-19 associated CNS dysfunction.

2.9.8. Interleukin-17 (IL-17)

IL-17 (6p12.2) is a pro-inflammatory cytokine secreted by Th17 and CD8 cells, involved in many physiological and pathophysiological conditions. *IL-17* expression is associated with the severity of COVID-19 patients in several studies [75,94–96]. A higher number of CCR6 + Th17 cells are found among severe COVID-19 patients [97]. Increased IL-17 signaling may affect neuronal toxicity by activating NFκB mediated inflammatory pathways [98]. IL-17 is mainly expressed in spinal cord astrocytes while IL-17RA is expressed in both astrocytes and microglia while ACE2 is also expressed in oligodendrocytes, astrocytes, neurons [27]. It indicates that SARS-CoV-2 may affect IL-17 mediated protective immunity to pathogens, and therefore, the IL-17 gene may contribute to neuronal toxicity and COVID-19-associated CNS dysfunction.

2.10. Endothelial cells and COVID-19-associated neurovascular damage

Endothelial cells, astrocyte and pericytes constituting the BBB and peripherally derived immune cells express *ACE2*. The presence of *ACE2* makes them an important target for SARS-CoV-2 through ACE2-S1 interaction. CNS endothelial cells (EC) and polymorphonuclear cells (PMNs) may contribute to inflammation after virus-mediated cytokine induction, consequently disrupting the blood-brain barrier. Therefore, it may contribute to early CNS toxicity or COVID-19-associated neurovascular damage (Fig. 4).

3. Summary

Four possible ways of CNS dysfunction and the development of COVID-19-associated disease has been discussed. It is possible that SARS-CoV-2 can manifest neurological complications through interaction with several cell types and regulators, such as [1] ACE2 expression in CNS cells make them vulnerable for COVID -19 associated neurological damage. 2) ACE2 expressing immune cells can mediate COVID-19 associated CNS injury. 3) Immune associated genes may mediate mechanisms of COVID -19 associated neurological disease 4) Endothelial cells expressing ACE2 can lead to COVID-19 associated neurological damage. Further laboratory and clinical studies related to immune-associated genes in patients with COVID-19-associated CNS dysfunction should be conducted to understand its neuropathogenesis.

4. Future

Neurological complications of COVID-19 are not completely understood. Prospective multicentric studies should be carried out to collect cognitive, psychiatric, virological, and neurophysiological data from patients surviving severe COVID-19. This review will provide a useful insight and framework to understand COVID-19-associated neuropathogenesis. Present review could be helpful to find out the susceptible cell types to CoV-2 infection which may provide a better understanding of altered smell perception in COVID-19 disease. Furthermore, this review will be useful to design the expression studies related to the above-mentioned genes in patients with COVID-19 associated neurologic complications for better understanding of neuropathogenesis caused by COVID-19 disease.

Ethical approval

Not required.

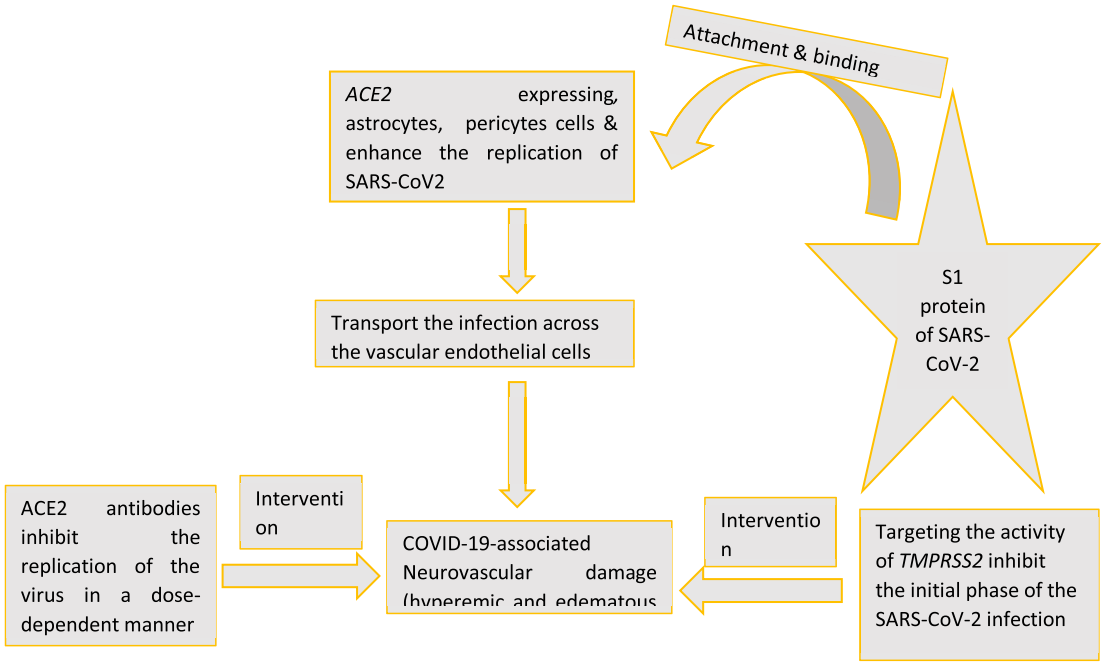

Fig. 4. Association of endothelial cells and COVID-19-associated Neurovascular damage.

Funding source

Not required.

Conflicts of interest

No.

Data availability statement

Data will be available on request by email.

Authors contribution

HariOm Singh: Overall supervision, **Amita Singh:** Manuscript writing, **Abdul Arif Khan:** Review of manuscript, **Vivek Gupta:** Manuscript Review.

Declaration of competing interest

There are no conflict among the Authors.

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