
بسم الله الرحمن الرحيم

عوارض عصبی شناختی کووید 19

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متخصص بیماریهای مغز و اعصاب
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Introduction

The coronavirus disease-2019 (COVID-19) outbreak, has rapidly spread worldwide

The pathogen responsible was identified as the 2019 novel coronavirus, is a member of beta coronavirus family,

which was subsequently renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

COVID-19, a probably bat originated disease was declared by World Health Organi-zation (WHO) as a global pandemic in March 2020.

Coronavirus (CoVs) are the largest group of viruses belongs to the Nidovirales order that comprises three families i.e. arteriviridae, roniviridae and coronaviridae

Coron-aviruses are 60 to 140 nm in diameter and have 26–32 kilobases positive sense single stranded RNA genome connected to a nucleoprotein surrounded by capsid

Novel coronavirus enters cells using SARS-CoV receptor ACE2 Moreover, novel coronavirus uses transmembrane protease serine 2 (TMPRSS2) for priming spike (S) protein

Coronaviruses are enveloped, positive-stranded RNA viruses that mainly cause respiratory and gastrointestinal tract infections

SARS-CoV-2 is continuously evolving virus with crucial mutation identified in the receptor binding regions.

neuroinvasive and neurotropic potential of coronaviruses like SARS-CoV and MERS-CoV has been demonstrated in many previous studies . A similar mechanism is suggested for the SARS-CoV-2 also

PHYSIOPATHOLOGY

Virus spreads mainly from person to person through respiratory droplets or bits of liquid, mostly through sneezing or coughing

First step of any viral infection is the binding of some viral proteins with receptors expressed by host cells followed by fusion with host cell membrane

ACE2 has been speculated to be the ultimate target of spike protein of SARS-CoV-2.

ACE2 is a membrane bound metalloproteinase and was discovered in 2000

Initial target of virus include lung epithelial cells, where virus attach through its spikes to

cellular angiotensin con-verting enzymes 2 (ACE2) receptor

Clinical Manifstations

SARS-CoV-2 could be transmitted from person to person through close contact and respiratory droplets

and then enters lung epithelial cells by binding to angiotensin converting enzyme 2 (ACE2) receptor and there it undergoes replication and targeting host cells causing severe pathogenesis.

Majority of human population exposed to SARS-CoV-2 having fully functional immune system undergo asymptomatic infection while 5–10% are symptomatic and only 1–2% are critically affected and requires ventilation support.

These categories of patients also display cytokine storm due to dysfunctional immune response which brutally destroys the affected organs and may lead to death in some.

The clinical manifestations of patients with COVID-19, including fever, shortness of breath, cough, headache, myalgias, diarrhea, fatigue, sore throat, anosmia, ageusia, chest pain, hemoptysis, sputum production, rhinorrhea, nausea, vomiting, skin rash, impaired consciousness, and seizures

Older people and patients with underlying diseases had much higher fatality rates than those without any preexisting complications such as hypertension, diabetes, chronic respiratory disease, cardiovascular disease, and cancer

Diagnosis of COVID-19 infection

Two broadly classified techniques include, Real time reverse transcriptase polymerase chain reaction (rRT-PCR) based detection and serology-based detection. RT-PCR technique involves conversion of viral RNA genome into DNA, which is further amplified using specific primers set against defined targeted regions of viral genome. Major targeted regions of SARS-CoV-2 genome include nucleocapsid (N) gene, envelope (E) gene and ORF1ab gene regions

IgM increases within a week time. Later on, titer of IgG increases from day 4 post infection and reaches to its peak by day 14

the levels of IgM degrade very rapidly whereas IgG antibodies titer persist in the body for longer duration

parameters such as high sensitivity CRP levels, lactate dehydrogenase, alanine transaminase, erythrocyte sedimentation rate, decreased lymphocyte count (depletion of CD4 and CD8 cells and decreased IFN-c expression in CD4 T cells are linked with severe COVID-19, illustrating the cytokine storm.

the presence of intravascular coagulation associated with increased D-dimer and fibrinogen levels in some COVID-19 infection.

Treatment Strategies for COVID-19 Infection

chest X-ray (CXR) and computed tomography (CT) scan are considered as an essential tool in the detection of COVID-19 pneumonia during this pandemic.

Treatment Strategies for COVID-19 Infection

Currently available drugs are generally categorized according to their targets:

one acts on mode of entry of virus , other acts on inhibition of enzymes responsible for viral genome replication

Most strategies considered in the clinical trials aim to

accelerate the viral clearance and inhibit the cytokine storm to minimize the need for mechanical ventilation, long hospital stays, and COVID-19 associated mortality.

Combination of lisinopril and losartan treatment in normotensives, abolished increase in ACE2 mRNA levels observed individually but retained losartan induced rise in ACE2 activity in heart

different anti-inflammatory drugs such as tocilizumab, chloroquine (CQ)/hydroxychloroquine (HCQ), and dexa-methasone have been proposed to decrease or suppress the release/-production of pro-inflammatory cytokines with the aim to minimize the cytokine storm associated with

SARS-CoV-2

emergency treatment strategies include the use of remdesivir and convalescent plasma in the USA and favipiravir in China

importance of IFNs in the treatment of COVID-19

passive immunotherapy with the use of plasma from convalescent patients

Cytokine storm is one of the characteristic phenomena of SARS-CoV-2 infected patients. Initial evidences revealed that targeting anti-inflammatory molecules such as IL-6, IL-1R and TNF-a might be important in reducing the inflammation and ultimately inflammatory response. Currently, clinical trials have shown that tocilizumab (anit-IL-6), a humanized antibody significantly improves the clinical outcome of COVID-19 cases

Similarly, Ana-kinra (anti-IL-1R) is also important in decreasing the inflammation

Corticosteroids are well known anti-inflammatory molecules are effective for the treatment of a variety of inflammatory diseases

Mesenchymal stem cells (MSCs
intra-venous injection of N-acetyl cysteine
hypercoagulation stage in severe COVID-19 patients

Imatinib a tyrosine kinase inhibitor and colchicine, an anti inflammatory drug

Neurological Manifestations

regarding viral neuroinvasion, there are several routes for possible transmission, including trans-synaptic transfer across infected neurons in splacnic nerves, entry via the olfactory nerve, infection of vascular endothelium, leuko- cyte migration across the BBB, and/or a conjunctival route

From the olfactory bulb, SARS-CoV-2 may target the deeper parts of the brain including the thalamus and brain stem by trans-synaptic transfer described for many other viral diseases

More than 80 percent of hospitalized patients may have neurologic symptoms at some point during their disease course

since the SARS-CoV-2 can invade the central nervous system (CNS), thus causing a multitude of diverse neurological manifestations as acute cerebrovascular diseases, encephalopathy, seizures, acute hemorrhagic necrotizing encephalopathy, acute disseminated encephalomyelitis (ADEM) and transverse myelitis , acute polyneuropathy, Guillain Barre Syndrome (GBS) and its variants , hypogeusia, and hyposmia, as well as certain nonspecific symptoms (such as headaches, myalgia, fatigue and unsteadiness

headache, hypogeusia, and anosmia appear to precede the onset of respiratory symptoms in the majority of affected patients, and ataxia and altered mental status have been documented

Neurological symptoms may occur in their first 1 to 2 days of the clinical symptomatic phase, and cerebrovascular accidents are common within 2 weeks of the onset of the symptomatic phase

several features associated with infection and severity of the disease (ie, older age, hypertension, diabetes, cardiovascular disease) share a variable degree of ACE2 deficiency

detection of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF).

SARS-CoV-2 can also be found in the brain post mortem.

pan-encephalitis and diffuse petechial hemorrhage of the entire brain have been reported

respiratory problems due to SARS-CoV-2 are thought to be due in part to brainstem dysregulation, as are possibly some of the gastrointestinal symptoms.

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In some individuals, SARS-CoV-2 infection triggers a massive release of cytokines, chemokines, and other inflammation signals leading to BBB dysfunction, injury to astrocytes, activation of microglia and astrocytes promoting neuroinflammation and neuronal death. Immune response and excessive inflammation in COVID-19 may also accelerate the progression of brain inflammatory neurodegeneration,

elderly individuals are more susceptible to severe outcomes after SARS-CoV-2 infection

BRAIN IMAGING

Structural brain magnetic resonance imaging (MRI) revealed parenchymal brain abnormalities, subcortical micro- and macrobleeds, cortico-subcortical edema, nonspecific deep white matter changes, and asymmetric olfactory bulbs post mortem and similar findings during hospital admission

The abnormal imaging has been seen in an individual whose only symptom was anosmia

The most common MRI findings from patients admitted to ICUs include cortical signal abnormalities on

fluid-attenuated inversion recovery images, accompanied by cortical diffusion restriction or leptomeningeal enhancement, which may reflect infectious or autoimmune encephalitis, seizures, hypoglycemia, or hypoxia. Acute demyelinating lesions also have been described and have been visualized on images.

POSSIBLE DETERMINANTS

C- reactive protein and ferritin levels were associated with elevated risk of COVID-19 in a dose-dependent

manner, and N-terminal pro- brain natriuretic peptide (NT-proBNP) was associated with increased mortality in COVID-19 pneumonia

Concomitant cardiac disease has an extremely poor prognosis, with higher mortality, thrombo- embolic events, and septic shock rates.

Among hospitalized COVID-19 cases ,physical inactivity, smoking, and obesity but not heavy alcohol consumption were related to increased rates of hospital admission.

Diabetes mellitus increases risk for dementia as well as of severe outcomes after SARS-CoV-2 infection

The chronic neuropsychiatric sequelae of COVID-19

Because the entry points of viral invasion into the brain have direct connections to brain stem and thalamic structures, ensuing dysfunction may result in sensorimotor, mental, and behavioral disorders

acute alteration in personality, behavior, cognition, or consciousness was the second most common presentation of COVID-19, often occurring in younger individuals; nearly half of these individuals had new-onset psychosis, while the rest had neurocognitive (dementia-like) syndrome, or affective disorders

Direct effects of SARS-CoV-2 itself on neuronal function and survival or glial reactivity, exaggerated cytokine responses, or anti- neuronal antibodies are all likely to contribute, as are the sequelae from cerebrovascular accidents expectation of increased neuropsychiatric sequelae, including cognitive decline, motor impairment, and affective and psychotic disorders, in addition to demyelinating processes or cerebrovascular disease that occur during the acute viral infection, or may follow infection in recovered individuals.

Autoimmune encephalitides associated with antibodies against neuronal cell-surface or synaptic proteins; in those with new-onset psychosis, higher prevalence of antibodies against four other coronaviruses strains have been found, and at least one confirmed case of anti-n-methyl-d-aspartate antibodies encephalitis associated with COVID-19 was reported.

clinical-radiological features of limbic encephalitis and little systemic symptoms of COVID-19,suggests immune-mediated response to SARS-CoV-2

possible mechanism for SARS-CoV-2 encephalopathy and psychosis.

Delirium can be the only presenting symptom of SARS-CoV-2 infection)hyperactive delirium(

In elderly patients with dementia, delirium is a very frequent presenting symptom of SARS- CoV-2 infection

The incidence of delirium in severely ill COVID-19 patients on ICUs is reported to be as high as 84%, of which more than two thirds exhibit hyperactive delirium, despite receiving high sedation and neuroleptics

In elderly patients with dementia, delirium is a very frequent presenting symptom of SARS- CoV-2 infection90 and carries a higher short-term mortality rate

Delirium in COVID-19 may be a feature of primary encephalopathy due to the direct intracerebral viral invasion.

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Alternatively, secondary encephalopathy may be associated with neuroinflammatory response to SARS-Cov-2, immune-mediated systemic response, or independent complications of hypoxemia, sepsis, hypoperfusion, severe metabolic illness, and pharmacological side effects.

COGNITIVE DECLINE AND MOTOR IMPAIRMENT

COVID-19 results in high levels of proinflammatory cytokines, acute respiratory distress, and hypoxia, each of which may contribute to cognitive decline both in healthy and in already predisposed individuals

coronaviruses can cause demyelination, neurodegeneration, and cellular senescence.

SARS-CoV-2 specifically can infect endothelial cells expressing ACE2 potentially leading to further
deterioration of this vascular architecture.

The resulting hypoperfusion may restrict energy substrates essential for maintaining neuronal
.networks thereby accelerating cognitive decline in the elderly.
Viral entry into neurons may create a cytotoxic insult and initiate
–apoptotic pathways or create an excitatory
.inhibitory imbalance
This pathway is already postulated to play a role in several neurodegenerative diseases including AD and Parkinson's disease

A slow infiltration throughout the CNS may precipitate underlying pathologies associated with age-related neurodegenerative disorders months or years after acute viral infection.

MRI features of cerebral small vessel disease, ie, white matter hyperintensities, lacunes, microbleeds, perivascular spaces, and cerebral atrophy were additively associated with dementia and cognitive decline. Therefore, it seems likely to expect that COVID-19–related cardiovascular and cerebrovascular disease will also contribute to a higher long-term risk of cognitive decline and dementia in recovered individuals

viral infections of the brain may impact a person's risk for AD or Parkinson's disease. The present pandemic provides a unique, if unwelcome opportunity to test the role of neurotropic viruses in a prospective fashion in individuals that have recovered from COVID-19

After the coronavirus pandemics in 2002 and 2012, one in five recovered individuals reported memory impairment and an early report found that one in three individuals with COVID-19 had dys-executive syndrome at the time of hospital discharge

Impaired cognitive abilities may cause poor occupational and functional outcomes for individuals recovered from COVID-19 that precipitate or exacerbate mental health concerns, and poor mental health may likewise contribute to cognitive dysfunction

PSYCHIATRIC DISORDERS

Psychiatric distress and acquired cognitive deficits after COVID-19 will likely have complex, bidirectional relationships. Impaired cognitive abilities may cause poor occupational and functional outcomes that precipitate or exacerbate mental health concerns, and poor mental health may likewise contribute to cognitive dysfunction.

Patients with preexisting psychiatric disorders reported worsening of psychiatric symptoms. After the corona virus pandemics in2002and2012, one in five recovered individuals reported depressed mood ,insomnia, anxiety, irritability, fatigue, traumatic memories and sleep disorder were frequently reported.

CONCLUSION AND NEXT STEPS

The increasing evidence and understanding of SARS-CoV-2’s impact on the CNS raises key questions on the impact for risk of later
life cognitive decline, AD, and other dementia

Alzheimer’s Association and representatives from more than 30 countries with technical guidance from the World Health
Organization , have formed an international, multidisciplinary consortium to collect and evaluate the short- and long-term consequences of
SARS-CoV-2 on the CNS

This program of studies aims to better understand the long-term consequences that may impact the brain, cognition and functioning—including the underlying biology that may contribute to AD and other dementias

This consortium will link study teams from around the world covering more than 22 million cases at the time of submission
to enroll two groups of individuals including people with confirmed cases of COVID-19 sampled from hospitals that have
been discharged to be evaluated for follow-up at 6, 9, and 18 months, and people who are already enrolled in existing international research studies to add additional measures and markers of their underlying biology