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IMPACT OF COVID-19 IN ALZHEIMER'S PATIENT'S

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ABSTRACT

Due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes Alzhemer's disease a neurological complication of COVID-19. In AD patients multiple pathological changes such as the excessive expression of viral receptor angiotensin converting enzyme 2 and pro-inflammatory molecules may increase morbidity and mortality of covid 19. various neurologic symptoms like cognitive impairment has reported in covid 19 that may results in AD, SARS-CoV-2 may invade into the central nervous system, COVID-19- may induce inflammation, long-term hospitalization and delirium, and post-COVID-19 syndrome. In addition, uninfected AD patients behavioral symptoms may be worsen by covid 19 crisis and provide new challenges for AD prevention. In this review.we first know about the SARS-CoV-2 and AD-COVID-19.

KEYWORDS: COVID-19, SARS-CoV-2, Alzheimer's disease, Inflammation, Central nervous system.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that affect predominantly the human respiratory system and has also targeting central nervous system (CNS).[1,2] Incubation period is 5 days for SARS-CoV2, and the

symptoms are most likely to be of COVID-19 include fever, cough, and fatigue followed by or associated with headache, dyspnea, and hemoptysis.[1,2] For severe cases Acute respiratory distress syndrome, acute cardiac problems, pneumonia, and multiorgan failure had also been observed[1,2] Central nervous system is reported about 25% of COVID-19 patients have been reported.[3] Other atypical respiratory symptoms include headache, dizziness, anosmia, stroke, and deteriorated consciousness or memory,impaired mental state, delirium, and electrolyte and metabolic derangements have been noticed in some patients.[3] Among central nervous system (CNS) of COVID-19and Alzheimer's disease (AD) comorbidities stand first.[4] AD is a neurodegenerative disorder that affects memory and learning, behaviour, and cognitive performance of the patient. The hippocampus region of brain responsible for memory and learning processes becomes affected due to deposition of amyloid beta (Aβ) or neurofibrillary tangles (NFT) in the AD patients.[5] AD appear mostly after age 60, and the patients become dependent on their caregivers and family members.[5] As COVID-19 management needs isolation and quarantine, AD management needs attention to the patient always.[2–4] The COVID-19 may cause burden to AD patient, caregivers, and family members and on the national and global economy. Common etiological factors may manage the therapeutic approach on both COVID-19 and AD. In present review has been designed to know the common links between COVID-19 and AD so that scientists, healthcare providers, policy-makers, and the general readers would be benefitted in managing the already suffered patient and also to safeguarding the future generation.

SARS-CoV-2 and AD-COVID-19

Coronaviridae is the family of SARS-CoV-2 and it is a non-segmented envoloped positive-sense RNA virus. SARS-CoV-2 can spread directly through droplets, aerosol, and fomite into the human body includes neural parenchyma, the nasal mucosa, the lamina cribrosa, retrograde axonal transport, and the olfactory bulb.[6] The SARS-CoV-2 neurotropism charecter may be lead to invasion on the neural tissues by binding its spiked protein with angiotensin-converting enzyme 2 (ACE2) receptors present in the neurons and glial cells.[6, 7] In lungs, epithelium of the upper and lower airways of ACE2 mostly.[6,7,8] The heart, kidneys, and lungs consist of type I membrane protein ACE2 of renin-angiotensin systems. Spike (S) proteins of both SARS-CoV and SARS-CoV-2 form a trimer harbor of receptor-binding domain (RBD) that interacts with high affinity of lysine 31 on ACE2.[6–8] Compared with those of other SAR-COVs, 10–20-fold increased affinity of SARS-CoV-2 spike protein towards ACE2 are found.[8,9] On ACE2 receptor, SARS-CoV-2 may utilize the trans-synaptic

routesand olfactory bulb directly.[10,11] SARS-CoV-2 stimulateastrogliosis, microglial activation, and neuroinflammatory cascade. The blood–brain barrier (BBB) become affected due to systemic inflammation due to disruption of brain homeostasis and neuronal death.[11] Because of this infection of the brain stem might increase cardiovascular and respiratory regulation to chemosensory neural cells and cause respiratory failure results in intense hypoxia.[10,11] The Combination of hypoxia and neuroinflammation destroy the cortical and hippocampal function caused by neurological disorders. The direct Central nervous system SARS-CoV-2 causes inflammatory mediators and release increased BBB permeability and heightened hypoxia.[12] As the CNS is made of major histocompatibility antigen, it mainly depend on cytotoxic T lymphocytes for removal of virus. Mainly infected by toxic encephalopathy, acute encephalitis, and cerebrovascular attacks (CVAs).[12] Headache and seizure are caused due toacute encephalitis; delirium and coma are caused due toinfectious toxic encephalopathy while an increased risk of CVA is a manifested on SARS-CoV-2-provoked cytokine storm and coagulate abnormalities.[12] Neuronal expression of ACE2 may high the nACh receptor and it may help to stimulatethe nicotine, and makes the smokers much vulnerable towards neuropathological maladies.[13]

Relationship between SARS-CoV-2 and AD

Viral infection

Numerous studies related AD to viral pathogen.The herpesvirus family including herpes simplex virus (HSV) and human herpesvirus (HHV) is the most studied viral family for AD.[19,20,21] The results from this supported the hypothesis of epidemiological, post-mortem, animal, and cell-culture studies.[54] For example, results from a cohort study on population basis shows reactivation of HSV seropositivity is highly correlated with incident AD.[55] The damage on hippocampus as well as to the temporal and frontal lobes, are caused by HSV-induced herpes simplex encephalitis (HSE) on same brain areas that are affected in AD, to induce a cognitive phenotype related to AD.[56,57,58] Cognitive impairment may alsobe observed together with neuroinflammation.[59] The HSV-1 is the infection by the alteration of Aβ metabolism, calcium homeostasis dyregulation, synaptic dysfunction, and cultured human neuronal apoptosis and glial cells.[60] The anti-HSV drugs have been shown to reduce Aβ and p-tau accumulation in the infected mouse brains and all these findings suggest the strong association of HSV will be related to pathogenesis of AD. With HSV-1, multiscale analysis of three independent Alzheimer's cohorts studies carried out by Readhead et al. AD is aregulatory relationships of viral abundance and modulators of Aβ production.[19] The

pathologic effects of HHV-6A on AD are caused by the suppression of miR-155 and dysregulation of the autophagy and protein response.[19,21] These studies provide evidence for the contribution of specific viral species to develop the neuropathology and AD.

In note Aβ and NFT are the hypotheses of AD as known, although they do not entirely explain the pathogenic mechanism. Recent evidence have shown that neuroinflammation hypothesis, though the causality needs to be addressed.Now a days evidence has also implicate viral infection in AD, although future studies are done to identify the underlying mechanisms for how each specific viral infection leads to AD.

Inflammo-proteomics

The respiratory syndromes of SARS-COV-2 have got attention when neurological co-manifestations have received atleast more than one-third of the patients had neurological symptoms.[14] During the initial stage of illness most of the neurological symptoms had been manifested.[15] Inflammatory mediators have been implicated in CNS manifestations, and immunological process in peripheral nervous system (PNS) abnormalities, while skeletal muscle injury has been considered the direct effect of SARS-CoV-2.[10,16,17] The common link between inflammatory markers received most attention are interleukin 6 (IL-6), interleukin 1 (IL-1), cytoskeleton-associated protein 4 (CKAP4), and galectin9 are the common links between COVID-19 and AD manifestations.[18]

IL-6

Plasma level of inflammatory cytokines had been reported to be associated with AD progression and related with immune responses.[18] Like wise human cognitive performance had been inversely linked with chronic peripheral elevation of IL-6.[18] It may also form significantly increased level of plasma IL-6 is reported in 47 AD patients compared with their agedpatient.[19] The increase in acute-phase proteins in the serum of AD patients are initiative of compromised immunity. Memory and learning–related behavioral tests likeMorris water maze test, hole-board test, elevated plus maze test on mice revealed that the mice deficient of IL-6 retain improved reference and spatial memory and demonstrate a better cognitive performance.[20] Though exact mechanism has not been found yet, reduced IL-6 might mediate a signaling cascade involved in maintaining and restoring memory.[20] An increased serum level of IL-6 had been linked with increased COVID-19 death.[21] And also it linked for respiratory dysfunction.[22,23] Plasma protein of IL-6 is the most used proteins in COVID-19 patients and marked as an indicator of disease.[24] The increased serum IL-6 level is a

common indicator of respiratory complications occurred in COVID-19. In the replication of SARS-CoV-2 may elevate production of IL-6 and highrespiratory distress. Since the IL-6 stands biomarker for AD and COVID-19 as common. Antibodies capable of blocking the IL-6 receptor are tocilizumab and sarilumab which have been have been undergoing phase 2/ 3 clinical trials as the putative medications against COVID-19.[25] As inflammatory process of AD results in neurodegeneration that could be slowed down through reduced generation of IL-6, tenidap, a non-steroidal anti-inflammatory drug, had been found promising in AD therapeutics.[26] IL-6 is a pleiotropic biomarker for CNS and respiratory system among which AD and COVID-19 worth mentioning. IL-1 is higher in the COVID-19 patient during disease start and entire range of disease progression.[27,28]

IL-1

IL-1 is high in COVID-19 patient on starting stage of disease and entire range of disease progression.[27,28] Anakinra, an IL-1 receptor antagonist recombinant is found effective in improving clinical symptoms like respiratory distress in 72% cases.[27,28] Levels of IL-1 had also been reported high in AD patients.[29] Impaired long-term potentiation and consolidation of memory and learning processes had been associated with increased IL-1 level.[30] Injection of IL-1β shows increased Aβ and NFT production in rat brain.[31] And also blocking of IL-1 had been found AD ameliorating.[32]

GAL-9

Gal-9 is a β-galactoside-binding protein it include immune reaction regulation. Its increased production had been associated with viral infection in the lung.[33] The therapeutic strategies include suppressing Gal-9 production in COVID-19 pandemic.[34] Gal-9 in the CNS had been reporte to be a facilitator of oligodendrocyte maturation and myelin repair mechanism.[35] Increased level of serum Gal-3 had been shown in AD patients.[36] Galectin-3 is a promoter of Aβ oligomerization and toxicity in AD animal models.[37] Galectin-3 is also an inflammatory marker whose modulation are promising in COVID-19 and AD therapeutics.

ApoE4 Allele

Apolipoprotein E in the central nervous system (CNS) is the main carrier of cholesterol and also an important constituent of very low–density lipoproteins (VLDL). The three alleles are ε2, ε3, and ε4 which carry the ε4 allele are at a high risk of developing AD as the ApoE ε4 or ε4 genotype increases fibrinogenesis in the brains of Alzheimer's disease patients.[41] ApoE4 has reported in cerebral hemodynamics such as leakage of the blood–brain barrier and

cerebral amyloid angiopathy.[41] APOE4 is a marker increasing COVID-19 severity.[42,43] AD patients carrying the APOE4 allele are at a high risk of developing COVID-19.

ACE2 Upregulation

Ten times elevate expression of ACE2 gene, SARS-CoV-2 binding protein for cell entry, had been found in the brain tissues of the AD subject compared with those of their age-matched non-AD individuals.[44] AD patients are at a high risk of COVID-19 comorbidity.

Nitric oxide level

Nitric oxide (NO) is an endothelium-derived relaxing factor and a neurotransmitter, plays an important role in memory and learning process and thus aids in maintaining behavioral and cognitive normalcy.[45] SARS-CoV-2, binding with the vasoconstrictor type 1 angiotensin II receptor (AT1R) which is overexpressed on ACE2, might lower NO production on cerebral neurons. As COVID-19 patients would become much vulnerable to behavioral and cognitive decline, the manifestations of AD.[46]

Cross-talk Between AD and COVID-19

Not only to the above mentioned similarity, there exists some disparity-oriented discourse between AD and COVID-19[67] For example, headache, cough, and seizures are common features of COVID-19 but not of AD Some other contrasting features may also been seen.

Age

Older people are at a higher risk of having both AD and COVID-19.[68] But, for patients aged over 80 years, further ageing is not a risk factor for COVID-19, rather for dementia and AD.[68] On the other hand, AD susceptibility usually begins on or after 60 years of age and as aging advances, the AD become worse.[69] Increased production of reactive oxygen species (ROS), exacerbate amyloid beta, aggregate and neurodegeneration, perturbed proteostasis, cardiovascular diseases (CVD), diabetes, hypertension, and lifestyle modification had been implicated in AD pathogenesis of the aged persons.[69]

Sex

Compared with females, males had been found much increased in COVID-19 fatality.[70] Increased ACE2 level may have effect on testosterone on ACE2, imbalance among ACE2 products (Ang 1–7, Ang 1–9), and dire onslaught of cytokine storm are among the possible factors affects men much than that of women.[70] Thus, manipulation of ACE2 expression

through sex hormone modulators seems penetrate in treating COVID-19. The estrogen and testosterone levels had been found neuroprotective and amyloid beta–clearing agents.[71] In females AD patients 80 years older, brain levels of androgen and estrogen had been found lower than their age-matched non-AD counterpart.[72] In case of normal and AD male the level of androgen and testosterone had been observed as aging progresses over 70 years.[72, 73] The sex hormone level contribute to the AD or COVID-19 in men and women. Keeping pace with this fact, treatment strategies might be formulated to sex hormone levels in many patients.

Treatments on covid-19 and AD

AD and COVID-19 differ in their pattern. AD is caused by deposition of Aβ or NFT abnormally a higher levels. The treatment strategies against AD focus mainly on Aβ production and its its clearance.[74] COVID-19 is caused by SARS-CoV-2 by entering into host cell cause inflammatory, respiratory, cardiovascular, CNS, and psychological complications. Thus, COVID-19 treatment strategies include impede viral entry, viral replication, and subsequent symptom amelioration. In this SARS-CoV-2-directed drugs likeremdesivir, lopinavir, host-targeting agents such as ACE or ACE2 receptor inhibitor, angiotensin receptor blockers (ARB), and immunomodulators such as inhibitors to IL-6 and IL-1, and plasma therapy had been in practiced grobally.[75]

CONCLUSION

In the recent COVID-19 disease the long-term consequences have been shaking the healthcare professionals globally. Alzheimer's disease stands among the top-notch on recent COVID-19 pandemic. Etiological and physiological factors described in this review would make us understand the stratergy of therapeutic algorithm against both COVID-19 and AD. We must understand that we have depend on only the data available recently and we must look towards future data from the scientific community to hold back the global crises like COVID-19 and AD.

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