



Effect of covid-19 on pathogenesis of neurodegenerated diseases like: Alzheimer and Parkinson's disease

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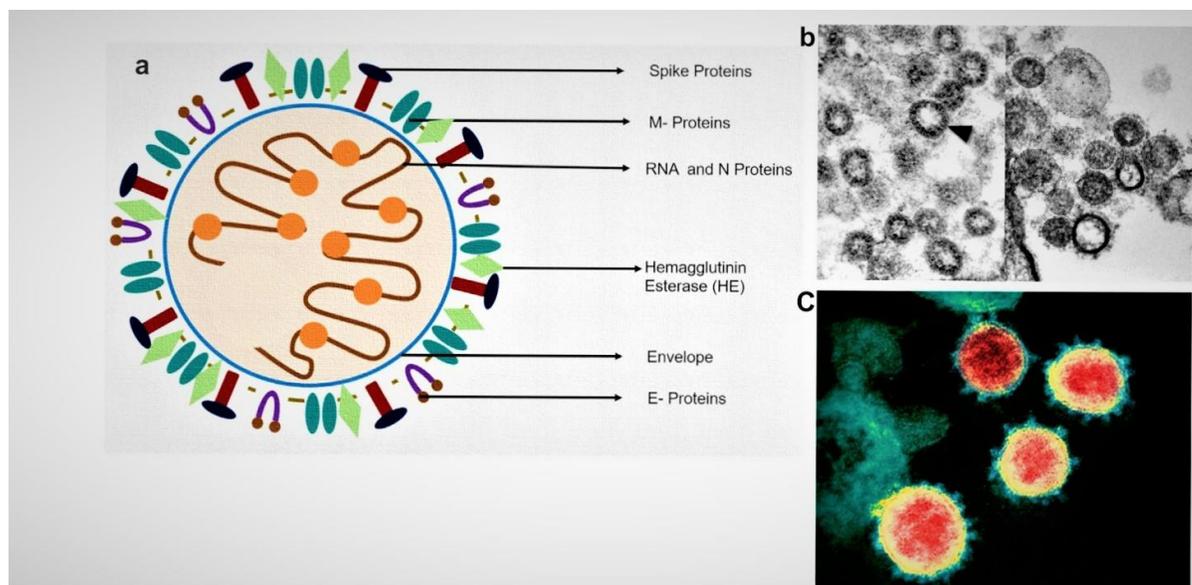
Abstract- acute severe respiratory syndrome Corona disease (SARS-CoV-2) is an HCV that has spread globally and caused the COVID-19 pandemic. This virus may enter human cells and harm the respiratory system of humans. However, several accounts of neurological symptoms point to a coronavirus development that is neuro invasive. Along with directly infecting neural cells, SARS-CoV-2 can harm the brain in a number of ways. Chronic inflammatory responses flood the brain with proinflammatory substances, harming the neural cells and resulting in brain ischemia that is linked to various medical conditions. Chronic inflammatory reactions flood the brain with proinflammatory substances that harm neural cells and cause brain ischemia, which is linked to various health problems. Neuropsychiatric and neurological symptoms of SARS-CoV-2 included cognitive decline, sadness, light-headedness, delirium, and restless sleep. These signs of nerve injury contribute to the development of neurodegenerative diseases and dementia. In patients with COVID-19, SARS-CoV-2 has been detected in brain necropsies and isolated from cerebrospinal fluid. Proinflammatory cytokines have been examined as a prognostic factor due to the related inflammatory reaction in certain COVID-19 patients. As a result, the pathogenetic function of the immune alterations seen in Parkinson's and Alzheimer's patients is also included. A significant pathophysiological component of neurodegenerative disorders (NDs), including Parkinson's and Alzheimer's, has been inflammatory events. The A load and tau hyperphosphorylation have both been made worse by the neuroinflammation seen in AD. The increased load of A is caused by the local microglial and other immune cells, which also play a role in tau phosphorylation and disease development. Similar to this, neuroinflammation is crucial to the development of Parkinson's disease. Numerous investigations have shown a relationship between PD pathogenic pathways and neuroinflammation. The course of neurodegenerative processes and the buildup of -synuclein are guided by the dynamic proinflammatory stage. A few viruses may also act as stimulators and cause an autoimmune reaction against -synuclein. Therefore, neurological problems in COVID-19 individuals cannot be completely ruled out. The SARS-CoV-2 virus's neuroinvasive effects, on blood-brain barrier, and eventual effects on patients with neurodegenerative illnesses including Parkinson's and Alzheimer's are the main topics of discussion in this review article.

Introduction- Millions of people lost their lives as a result of the SAARS' COVID-19 epidemic, which made life difficult for people all over the world [1]. There has been widespread psychological and emotional hardship as a result of the pandemic's global lockdown [2–3]. By changing the concentration of cytokines, the pandemic has caused changes in the CNS's homeostasis and begun to cause neurodegenerative disorders [4-5]. The blood brain barrier is crucial in preventing the entry of hazardous chemicals into the central nervous system [6–8]. According to two-dimensional and three-dimensional microscopic fluidic in vitro models, the spike in SAARS COVID-2 is what cause the human BBB's permeability to change [9]. Parkinson disease and Alzheimer's disease development are two of the most prevalent neurodegenerative illnesses discovered worldwide and share comparable causes. Numerous investigations revealed that COVID-19 patients had elevated levels of the inflammatory cytokines including TNF- and interlukin-6 [10]. Similar to

past research on Parkinson, elevated plasma IL-6 levels have been linked to a higher chance of developing the illness [11]. Parkinson's disease and Alzheimer's disease can both be greatly helped by medicinal herbs like withania somnifera, mucuna pruriens, and tinospora cordifolia as well as their active ingredients like ursolic acid and chlorogenic acid. According to recent evidence, such plants and their contents are crucial in preclinical and clinical research for the treatment of COVID-19 patients [12–18]. The motor symptoms are getting worse as a result of SAARS' COVID-19, according to a recent study. A retrospective study indicated that the deterioration of symptoms with a considerable increase the development of motor neuron illnesses caused by SAARS' COVID-19 [19]

SARS Covid 19 structural study-

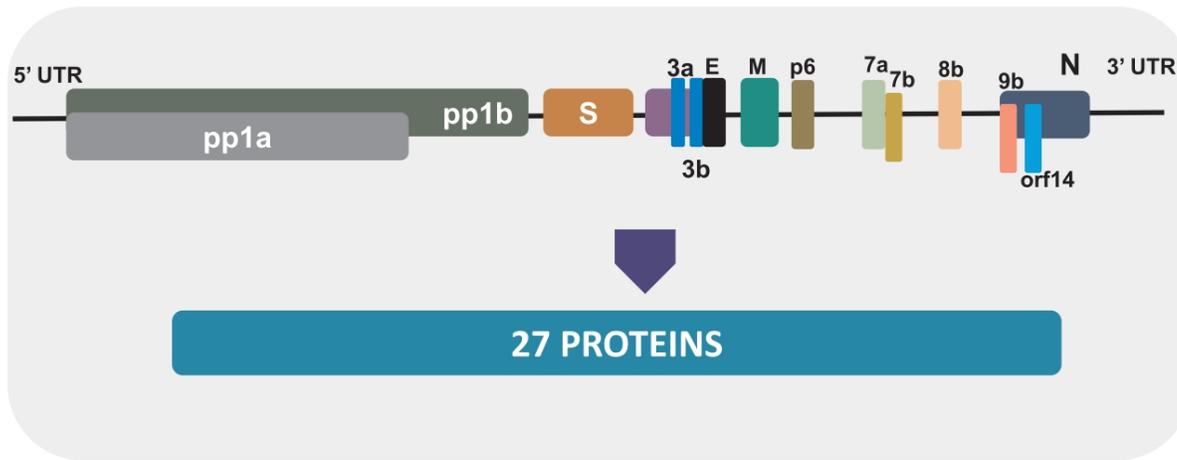
In Latin words corona means crown Because they contain spike glycoproteins on their membrane, coronaviruses appear like crowns under electron microscope (EM). It corresponds to the Nidovirales order and Coronaviridae family. Coronaviruses may be divided into several categories, including the alpha, beta, gamma, and delta groups. (HCoV-OC43) Human Coronavirus OC43 Severe acute respiratory, HKU-1, MERS-CoV, and SARC-CoV-2 are examples of -coronaviruses. Human Coronavirus-229E (HCoV229E) and Human Coronavirus NL63 (Sars - cov) are examples of -coronaviruses. The SARS-CoV-2 is a novel coronavirus (nCoV-2019), a new strain of the coronavirus family that has not before been discovered in humans. According to speculation, COVID-2019 may have been spread from bats to people via pangolins [20,21]. In immune-compromised people, symptoms of COVID-19 infection frequently include fever, breathlessness, and muscular discomfort a dry cough. When this infection is severe, it can result in bronchitis, pneumonia renal failure, and even death. By finding viral RNA and N protein in autopsy samples, this localization was discovered [22]. SARS-CoV-2 genome and proteome-



a) Labelled with spike protein, M-proteins, HE, E, & RNA containing nucleocapsid (N) proteins, the SARS-CoV2 structure.

b) SARS-CoV2 is shown with an arrowhead on transmission electron microscopy (TEM) pictures; image source: Centers for Disease Prevention and Control (CDC)|CS Goldsmith and TG Ksiazek (left), and NIAID (right).

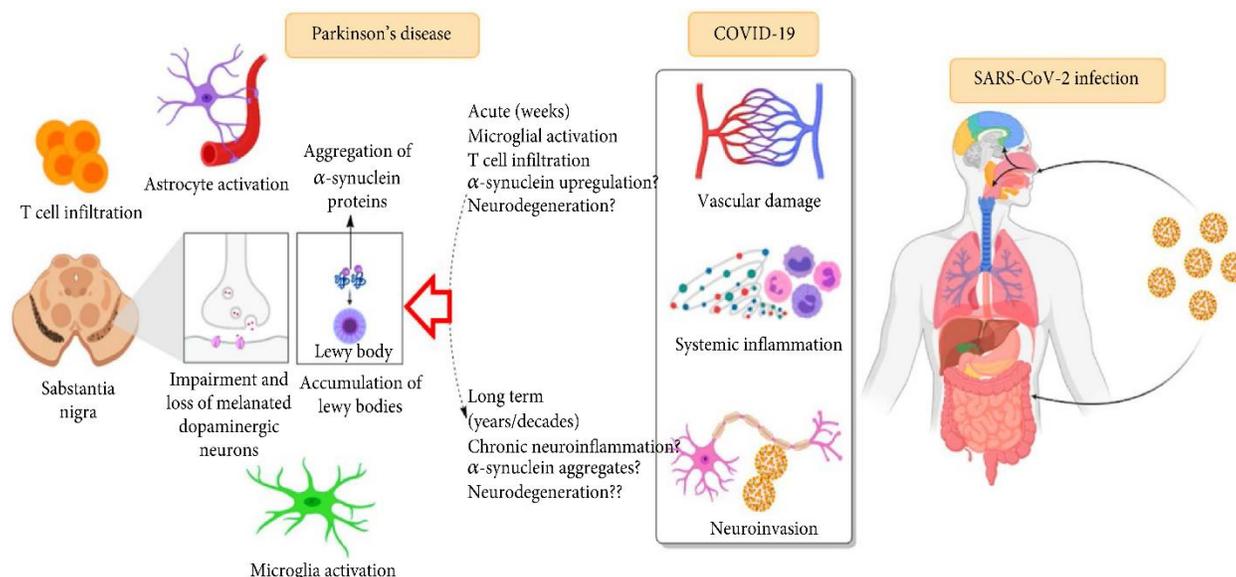
c). SARS-CoV2 (COVID-19) colored TEM with pronounced spike proteins on the envelope; photo credit: INSTITUTES OF HEALTH/SCIENCE PHOTO LIBRARY.



SARS-genome CoV2's was first discovered in China: The RNA genome of the SARS-CoV2 (IVDC-HB01/2019 (HB01) strain) is organized with pp1ab and pp1a proteins. The biggest gene, "orf1ab," codes for the "pp1ab" protein, which contains nsp1-nsp10 and nsp12-nsp16 (15 nsps). "Orf1a" also codes for the "pp1a" protein, which also contains nsp1-nsp10, which is another protein (10 nsps). The four structural genes—spike (S), envelope (E), membranes (M), and nucleocapsid (N)—encode structural proteins. Non-structural Protein Sequence (NSPS), Open Reading Frame (ORF), Source: Adapted from the Cell Host Microbe. 2020 March 11;27(3):325-328 by Wu et al.

impact of COVID-19 on pathogenesis of Parkinson disease –

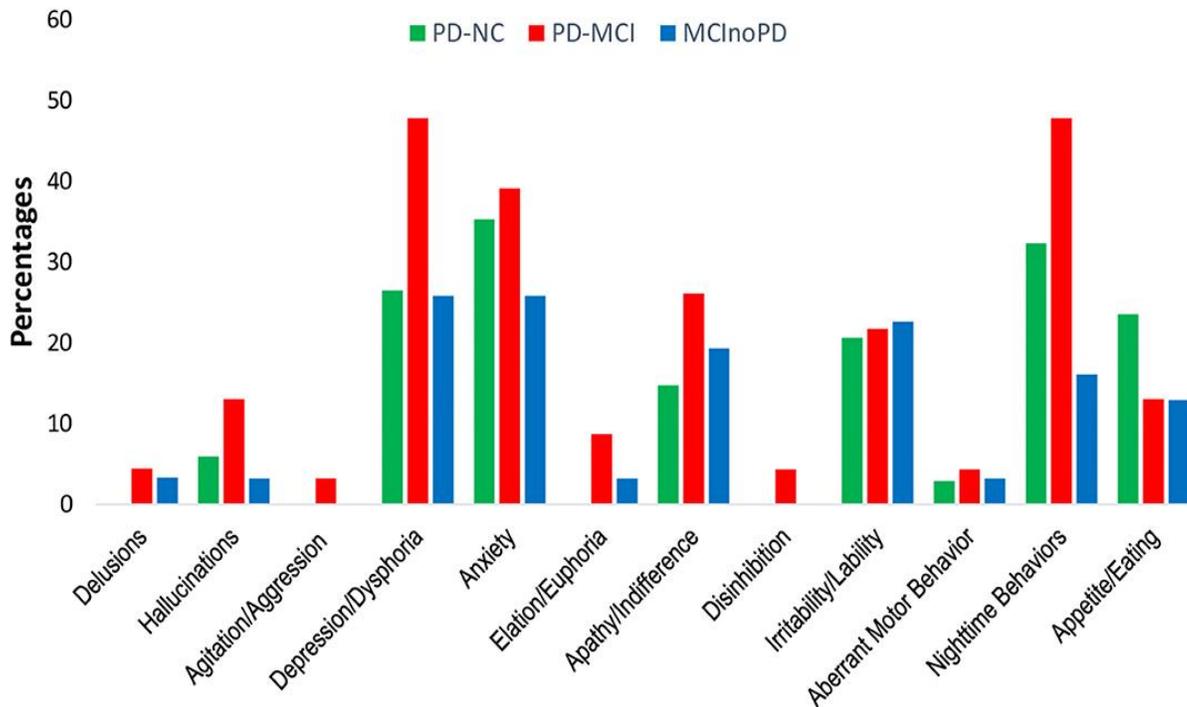
before COVID-19 diseases, various neurotropic viruses were already recognized, i.e., poliovirus, herpes simplex virus (HSV), influenza A virus, and members of the Coronaviridae virus family were previously identified before the COVID-19 pandemic [23-24]. The presence of viral protein and RNA in the brain tissue of individuals with COVID-19 infection during post-mortem investigations clearly suggests that SARS-CoV-2 also exhibits neurotropic features [25-26]. It has also been shown in the past that viral infections and parkinsonism are related. The post-encephalitis parkinsonism that occurred during the Spanish Flu (influenza A strain H1N1) pandemic in 1918 is the most often cited example of such a connection [27]. Nearly all individuals with encephalitis during an influenza virus infection had symptoms. A parkinsonian. Additionally, those born among 1888 and 1924 were shown to have a 2-3-fold increased chance of having parkinsonism [28]. Four examples of SARS-CoV-2 infection-related parkinsonism in individuals without a history of prodromal PD symptoms were described by Ayele et al. All patients had hypo/anosmia, two had encephalitis symptoms, and one patient's MRI revealed bilateral pallidal lesions [29]. A instance of parkinsonism after osmotic demyelination syndrome during the period of Severe acute respiratory infection in an older diabetic woman was documented by Ghosh et al. [30]. There are still many unknowns about the origin of PD [31-32].



According to current thinking, PD has an impact on several bodily systems [33]. The brain's nigrostriatal neurons are mostly damaged or killed when the illness progresses, and striatal dopamine reserves are depleted. One of the prevailing theories contends that an increase in oxidative stress brought on by the buildup of too many reactive oxygen species causes the alpha-synuclein protein to accumulate in the form of cytoplasmic clusters recognized as Lewy bodies [34-35]. A concurrent dual-hit theory is put out, in which the first "hit" is defined as the entry of an "unknown virus" into the brain through the gastrointestinal tract or the olfactory system. The infection causes glial cells to become activated, increasing the brain's susceptibility to oxidative stress, hastening brain ageing, and promoting neurodegeneration. According to certain investigations, SARS-CoV-2 could be one of these pathogens [36]. Alpha-synuclein levels may rise as a result of SARS-CoV-2 neuro infection [37]. One of the main components of Lewy bodies is the presynaptic protein alpha-synuclein, which is expressed, among other places, in the substantia nigra and thalamus. Research has demonstrated that the impairment of voluntary motor control caused by the degradation of nigrostriatal neuronal cells in PD is influenced by alpha-synuclein protein aggregation, oxidative stress, and glial cell activation [38]. Infection with the West Nile or Equine Encephalitis viruses has previously been linked to similar findings. There is proof that animals with lower neuronal alpha-synuclein levels were more prone to have encephalitis brought on by the West Nile virus. Altogether, it's possible that alpha-synuclein prevents the transmission of viruses [39-40]. Experimental investigations shown that aggregation formation that is typical of neurodegenerative illnesses, including Parkinson's disease (PD), is promoted by a chronically increased amount of alpha-synuclein [41]. The presence of the SARS-CoV-2 nucleocapsid protein was found to speed up the development of alpha-synuclein aggregation (N-protein) [42]. The so-called cytokine storm and systemic inflammatory response frequently play a significant role in neurodegenerative and SARS-CoV-2 infection. According to studies, SARS-CoV-2 interacts with the ACE2 receptors as well as transmembrane serine protease-2 (TMPRSS2) to enter cells [43-44]. The outcome is an increase in blood angiotensin II levels, which activate inflammatory cytokines like interferon-gamma and exacerbate the cytokine storm [45-46]. In severe COVID-19 instances, higher concentrations of (IL-1beta) interleukin beta, interferon gamma, interferon-induced peptide 10, as well as monocytic chemoattractant binding protein were found. The cytokine storm also includes IL-1, IL-2, IL-6, and tumor necrosis factor-alpha (TNF-alpha), whose impacts on the central nervous system have previously been demonstrated [47-48]. It appears that there is a clear connection between COVID-19 and the renin-angiotensin-aldosterone (RAAS), as well as PD. The involvement of ACE in Parkinson Diseases was shown by several research [49]. Patients enhanced motor responses to the dopaminergic precursor 3,4-dihydroxy-1-phenylalanine when treated with the ACE inhibitor perindopril [50]. Model ACE inhibitors in animals were discovered to offer defense against the death of dopaminergic neurons [51]. According to neuropathological investigations utilizing alpha-synuclein immunostaining, PD may start in the olfactory or gut neurons before spreading to the brain. Hyposmia and hypogeusia, which are frequent COVID-19 symptoms and also prodromal PD symptoms, suggest that SARS-CoV-2 has immediate access to brain areas important for PD [52]. Another idea contends that the gut microbiota is the starting point of the inflammatory process that results in PD. Gut dysbiosis can be caused by immune system deficiencies or an unbalanced gut microbiota. Increased intestinal permeability and bacterial translocation to distant organs including the brain are encouraged by local inflammation. Neuroinflammation is caused by the blood-brain barrier being disrupted by bacterial products. AS a result, a cycle is created that attracts and activates peripheral immune cells, further accelerating neurodegeneration [53]. Compared with the healthy control group, patients with COVID19 have changed gut microbiomes, which are referred to as dysbiosis inside the bacterial microbiome as well as mycobiome [54-55]. A community-based case-control research by Clira et al. on the symptoms of COVID-19 on Parkinson's disease (PD) revealed a substantial influence of SARS-CoV-2 on the worsening of both motor (including motor impairment) and non-motor PD signs [56]. Erro R. identified two cases of extreme dyskinesia (one of hallmarks of parkinsonism) following administration of the BNT162b2 (Drug company; Pfizer, York City, NY, USA; BioNTech, Mainz, German) mRNA vaccine. PD had previously been diagnosed in both patients, who were both ladies older than 60. (5 or 11 years prior to vaccination) [57]. According to authors, a systemic inflammatory reaction may have caused the symptoms that were reported. In vitro studies have demonstrated that the SARS-CoV-2 N-protein speeds up the aggregation of alpha-synuclein. Such a reaction, based on the experiences with West Nile virus, it may be argued that in a live body there exists a natural defense against the spread of viruses. In addition, alpha-synuclein buildup in the nigrostriatal dopaminergic pathway causes neurodegeneration, which is clinically evident as the usual PD/parkinsonian symptoms. Therefore, it may be assumed that similar motor symptoms may be caused by the CNS invasion of SARS-CoV-2. it also found that the virus makes use of the common ACE2 transmembrane receptors, which can be found in the intestinal nerves and olfactory pathway, which are both common primary sites for alpha-synuclein aggregates in PD and COVID-

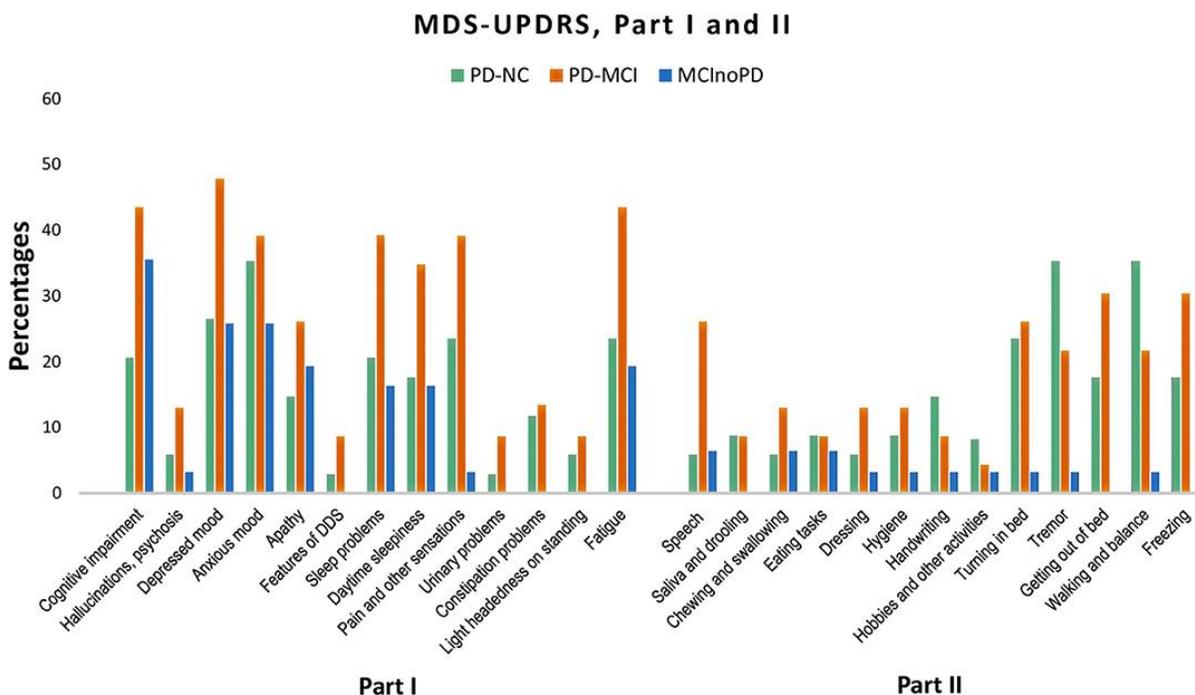
19. The cytokine storms and the inflammatory reaction may have a role in the development of all the illnesses, according to quite extensive data. Once more, the renin-angiotensin system is responsible for the start of the proinflammatory cytokine cascade. Contrarily, it was shown that PD patients using ACE inhibitors responded better to dopamine analogues; in animal models, ACE inhibitors prevented the death of dopaminergic neurons.

Neuropsychiatric Inventory



Changes in NPI in PD-NC, PD-MCI and MCIInoPD. NPI, Neuropsychiatric Inventory; PD-NC, Parkinson's disease with Normal Cognition; PD-MCI, Parkinson's disease with Mild Cognitive Impairment; MCIInoPD, Mild Cognitive Impairment not associated with Parkinson's Disease.

The current study assessed the effects of a 10-week lockdown during the COVID-19 pandemic in Italy on PD patients with or without MCI as well as on participants with MCI. The COVID-19 isolation made the cognitive, behavioral, and motor symptoms of PD and MCI patients worse. According to the caregivers' accounts, social withdrawal and isolation brought on by lockdown resulted in a material decline in cognition in almost 40% of patients, a worsening of NPS in 37.5% of cases, a new beginning of NPS in 26% of cases, and a decline in motor function in almost 35% of cases. As a result, in more than 25% of situations, the caregiver's workload increased during lockdown. Regarding the research groups' baseline characteristics, Patients with PD-MCI had a much longer illness. Longer than MCIInoPD. The latter, in terms of global cognition, group underperformed on the baseline MMSE test compared to PD-NC and PD-MCI, although this finding was only significant when compared to PD-NC vs. MCIInoPD. Likewise, a large variation within groups for BADL & IADL were discovered, with PD-MCI demonstrating the most activities were lost as compared to PD-NC. MCIInoPD, too. Considering the traits of the careers, within groups, there were no discrepancies. First, by contrasting patients with PDNC vs. PD-MCI, the impact of cognitive problems in PD during the COVID-19 lockdown phase was investigated. According to multivariate logistic regression analysis, PD-MCI was substantially and favorably correlated with the number of IADLs lost during the quarantine period. In addition, PD-NC patients had significantly greater Itel-MMSE score than PD-MCI patients, which was to be predicted. The two PD groups' deteriorating cognitive, behavioral, and motor symptoms, accelerated disease progression, and greater caregiver burden were not substantially different. After the lockdown phase, the impact of quarantine in participants with PD was mostly related to cognitive impairment in terms of NPI & MDS-UPDRS Parts I & II performance. In fact, there was no difference between PD-NC and PD-MCI in terms of motor symptoms, although the latter had much greater rates of cognitive problems and speech problems than the former.



Changes in MDS-UPDRS Part I and Part II in PD-NC, PD-MCI and MCInoPD. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD-NC, Parkinson's disease with Normal Cognition; PD-MCI, Parkinson's Disease with Mild Cognitive Impairment; MCInoPD, Mild Cognitive Impairment not associated with Parkinson's Disease. DDS, Dopamine Dysregulation Syndrome.

Only one research that compared motor and non-motor symptoms in participants with or without the infection to assess the impact of COVID-19 on PD patients is known to the authors of the current investigation [20]. The COVID-19 group's clinical symptoms dramatically worsened, according to those authors, albeit just minimally affecting cognitive ability. In the following, the impact of motor symptoms in MCI throughout the COVID-19 lockdown has been evaluated by contrasting it to MCInoPD against people with PD-MCI. Analysis using several logistic variables shown that PD-MCI was considerably and favorably correlated with an increase in symptoms, with a greater caregiver workload compared to MCInoPD as a result, PDNC vs. MCInoPD comparisons also supported this conclusion. The COVID-19 linked has worsened cognitive, behavioural, or motor symptoms in PD individuals, especially in PD-MCI, according to the findings of the current study. To this purpose, the location tracking and care of cognitively impaired patients during confinement as a result of the COVID-19 epidemic would benefit particularly from the use of telecommunication and digital technology equipment.

Other effects of Covid-19 in relation to Parkinson's Diseases-People with Parkinson's disease also have serious health problems as a result of Covid-19 [58-59]. Parkinson disease in people with COVID 19 is exacerbated by oxidative stress. For covid -19 patients, there will be both immediate and long-term effects [60]. Increased physiological stress therefore impairs a number of motor functions, such as dyskinesia and tremors, which raises the likelihood of Parkinson's disease [61-62]. Hypokinetic stiff syndrome is also brought on by elevated stress [63]. It has been shown in several animal studies that increased exposure to extreme stress may result in the death of dopaminergic cells. Parkinson patients' motor symptoms worsen and their dopaminergic cells were lost as a result of the covid-19 epidemic's reduced physical activity [64-65]. In addition, it contributes to non-motor problems including constipation and sleeplessness because of decreased physical activity [66]. According to evidence of the effect of covid-19 on Parkinson's disease put out by Chaudhry et al., simultaneous covid-19 infection and 6-hydroxytryptamine (6-OHDA) toxicity led to caspases-2, 3 and 8 being stimulated by the NF-KB pathway, which resulted in the death of dopamine-containing neurons [67]. They established a link between the inflammatory pathways that cause Parkinson's disease and SARS COVID-2 to produce oxidative stress. Numerous data point to the function that reactive oxide species and an underdeveloped antioxidant system play in the pathological development of COVID-19 disease and lung infection [68]. The TLR4-TRIF-TRAF6 pathways, that are activated by oxidative stress, have been identified as a pathologic inflammatory response route

that contributes to the irreversibility of chronic lung damage in several investigations. It has been demonstrated that the coronavirus promotes the caspase-based apoptosis necessary for viral replication [69]. By delaying apoptotic in virus-infected cells and assisting in the completion of the viral life cycle, the PI3K/Akt signaling pathway produced by a variety of viruses aids in the establishment of a chronic infection [70]. In light of this, PI3K/Akt signaling should be given considerable possible target in the fight against the COVID-19 pandemic. Additionally, it has been demonstrated that JNK, Akt, p38, oxidative stress, and NF- κ B signal pathways play a role in acute lung injury brought on by the influenza A virus (IAV); as a result, these pathways may potentially function as potential biomarkers in lung injuries brought on by COVID-19 [71]. As a result of the oxidative stress, which includes IAV-mediated TLR4 and NF- κ B signaling pathways, the host's inflammatory response may be exacerbated, resulting in acute lung injury. These results demonstrate that oxidative stress should be a focus of future study since it may be the common factor that links. FOS, FTH1, and PRDX1 are three genes with specific oxidative stress and extraordinary rise. The findings point to a connection between oxidative stress, inflammation, and the pathogenic COVID-19 infection process. The viral infection has traditionally been considered a risk factor for long-term neuron loss and PD development. Studies have demonstrated the effects of malfunctioning mitochondria, overexpression of mitochondrial genes, and genes that react to oxidative stress (a crucial component of neurodegenerative illnesses) in cells collected from COVID-19 patients. A COVID-19 investigation found that defective mitochondria produce proinflammatory mediators (, CCL3, CCL4, and CXCL-8, IL-6, CCL20, IL-12) [72]. Chemo-attractants, such CXCL-8, which are proinflammatory cytokines, encourage neutrophil infiltration and therefore contribute to the production of ROS and the activation of proteases, both of which furthermore promote to mitochondrial dysfunction [73]. Similar to this, the focus has remained on the COVID-19 disease due to the activation of a strong basic proinflammatory response. Men with high plasma IL-6 concentrations had a higher chance of developing Parkinson's disease, according to a case-control study [74]. It is previously known that TMPRSS2 and ACE2 have a role in SARSCoV-2 infection [75]. Similar to how it was in untreated rats, 6-hydroxydopamine, which is frequently employed as a tool to imitate PD, increased the expression of TMPRSS2 in treated rats [76]. Given that these proteins are variably regulated and essential in the development of diseases, our examination process reveals that genes may codify. It's interesting to note that people with PD have occasionally been linked to coronaviruses. The neurotropic nature of the COVID disease is thought to be connected to the respiratory symptoms it causes, with about 89% of patients in intensive care unable to breathe on their own. This appears to be the result of a central malfunction [77-78]. However, at the prodromal stage, when neurodegeneration has begun, gastrointestinal issues and hyposmia are the most prevalent non-motor symptoms in PD patients [79]. According to a retrospective analysis of COVID-19-infected patients hospitalized in Wuhan, China, 78 of the 214 patients may have neurologic symptoms, poor memory, and cerebrovascular disease occurring in the more severe instances. Patients with COVID-19 frequently report experiencing dysgeusia and anosmia [80]. These studies provide credence to the idea that coronaviruses like SARS-CoVs can penetrate human brain tissue.

impact of COVID-19 on pathogenesis of Alzheimer diseases–

With no effective treatments, AD is the leading cause of dementia and a global public health problem. Its uncertain pathogenesis is partly to blame for the lack of a viable cure. Several theories have been put forth to clarify the AD's mechanism.

A β -

According to the A hypothesis, senile plaques are created in the brain when A-40-42 accumulates due to the successive cleavage of the precursor of amyloid (APP) by either - or -secretase. Identifies the main pathogenic process. Genetic evidence supports the A hypothesis. For example, familial AD mutations of APP & PSEN1/2, which encode two essential -secretase complex components, are involved in either A generation or A processing and cause excessive production of A40-42 [81]. In contrast, an APP missense mutation (A673T) causes a lifelong decrease in APP cleavage by secretase, offering a lowered clinical risk of AD [82]. Interestingly, recent research has found that fibrillar A accumulated in dense plaques is less hazardous than soluble A oligomers. The A oligomers isolated from AD brains can decrease long-term potentiation and harm cultured neurons' synapses, dendritic spines, and neurons [83]. An oligomer can also cause tau to be hyperphosphorylated and the development of NFT [84]. Plaques can therefore act as "reservoirs" for soluble A oligomers to cause subsequent pathogenic events.

Tau-

Neuronal and synaptic degradation occur concurrently with NFT formation, therefore the clinical the NFT pathology is often strongly related to the characteristics and severity of AD [85]. NFT formation and tau hyperphosphorylation often follow the senile plaque development, showing that NFT is downstream A-accumulation cascade. However, Recent research has shown that tau events function independently since tau genetic mutations can result in frontotemporal dementia (FTD) even in the absence of A plaques [86]. This shows both tau and A may cooperate to increase their mutual toxicity and cause AD.

Nitric Oxide Level-

Nitric oxide (NO), a neurotransmitter and calming agent generated from the endothelium, is crucial for memory and learning processes and helps to maintain behavioral and cognitive normality and play very important role in Alzheimer diseases. [87]. SARS-CoV-2 may reduce the NO generation of cortical neurons via interacting with the vasoconstrictor type 1 angiotensin Receptor receptors-2 (AT1R) through overexpressed ACE2. As a result, COVID-19 individuals would be significantly more susceptible to cognitive and behavioral deterioration, which are AD's hallmark symptoms [88]. Nitric oxide synthase is an enzyme that breaks down L-arginine to generate NO, a tiny gaseous molecule (NOS). NO was described as an unusual neurotransmitter in the central nervous system (CNS) since it is not kept in vesicles and instead may serve as a retrograde transmitter when it is produced, moving from the post to the pre-synaptic neuron. NO participates in a variety of physiological processes, including vasodilation, inflammation, neuroprotection, neurotoxicity, and synaptic transmission [89]. After attaching to its biological receptor, soluble guanylate cyclase (sGC), NO exerts its effects either directly or by S-nitrosylation, a posttranslational modification that controls the activity of substrate. After attaching to its biological receptor, soluble guanylate cyclase (sGC), NO exerts its effects either directly or by S-nitrosylation, a posttranslational modification that controls the activity of substrate proteins and results in the creation of The second messenger cyclic guanosine monophosphate (cGMP), which is produced from guanosine triphosphate (GTP), is stimulated by the binding of NO to sGC. The transcription factor (cAMP) cyclic adenosine monophosphate response element-binding element (CREB) is then activated by the downstream effector protein kinase G (PKG), which in turn promotes synaptic plasticity, memory formation, and neurotransmission [90-91]. PKG also stimulates the Akt/PI3K signaling pathway, which prevents apoptosis and thereby promotes neuroprotection [92-93]. Additionally, NO could function at the presynaptic neuron by activating the sGC/cGMP/PKG pathway to encourage the release of neurotransmitters like glutamate [94].

GAL-9-

Gal-9 is a β -galactosidase-binding protein involved in immune reaction regulation. Its increased production had been related with viral infection especially in the lung [95]. Thus, therapeutic strategies aimed at suppressing Gal-9 production seem pertinent in COVID-19 pandemic [96]. In the CNS, Gal9 had been reported to be a facilitator of oligodendrocyte maturation and myelin repair mechanism [97]. Increased level of serum Gal-3 had been reported in AD patients [98]. Galectin-3 had been reported to be a promoter of A β oligomerization and toxicity in AD animal models [99]. Thus, galectin-3 is an inflammatory marker whose modulation seems promising in COVID-19 and AD therapeutics.

ApoE4 Allele-

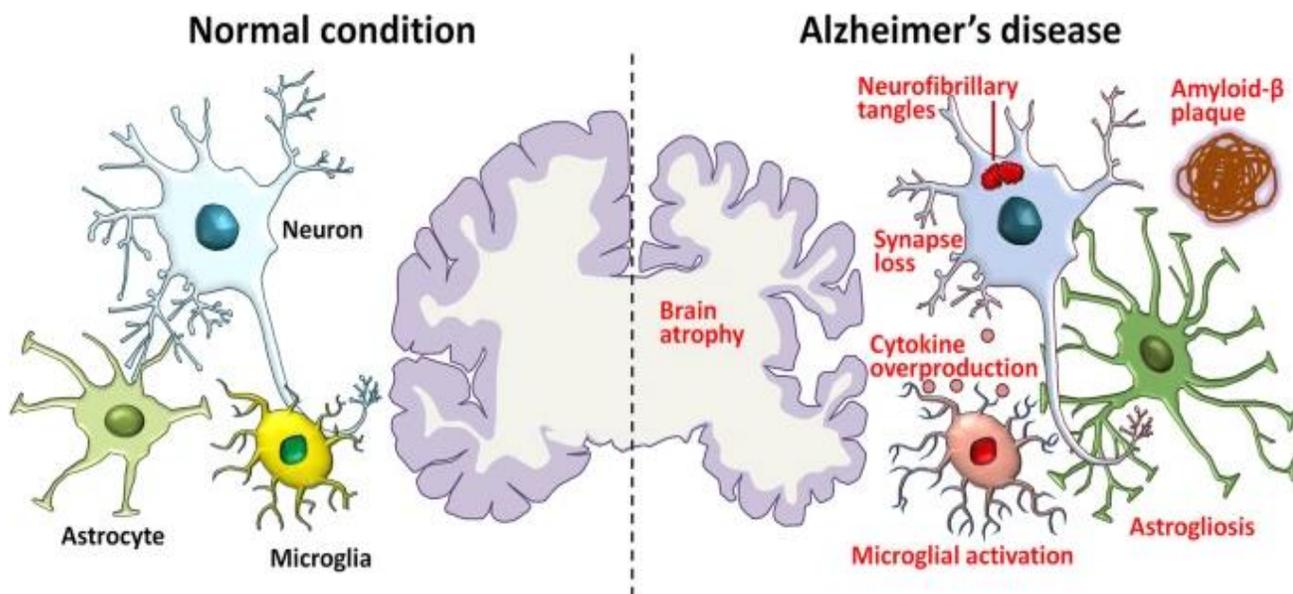
Allele apoE4 Apolipoprotein E is a crucial component of very low-density lipoproteins and the primary transporter of cholesterol inside the central nervous system. (CNS) (VLDL). Among its three alleles (2, 3, and 4), those with the 4 allele have a higher chance of developing Alzheimer's disease (AD) because the ApoE 4/4 genotype enhances fibrinogenesis in Alzheimer's patients' brains [100]. Additionally, it has been shown that ApoE4 affects cerebral hemodynamics, including blood-brain barrier leakage and cerebral amyloid angiopathy. APOE4 had recently been identified as a marker that increases the severity of COVID-19 [101-102]. Thus, COVID-19 is more likely to occur in AD patients who have the APOE4 genotype.

Anosmia

Anosmia, the inability of detecting smell or taste, is a hallmark of COVID-19 [103]. Anosmia or its relevant marker hyposmia, lowered sensitivity to detect smell or taste, is also a hallmark AD [104]. Anosmia might arise either from infection or blocked nose or due to degeneration of the nasal olfactory receptor neurons [105]. Importantly, brain injury leading to olfactory nerve or system damage may also manifest in anosmia. Recently, a diminished Zn²⁺ level had been linked with COVID-19 comorbidity of anosmia. SARS-CoV-2-induced local deficiency in nasal cellular zinc level might hamper the activity of Zn²⁺-dependent carbonic anhydrase, the enzyme responsible for olfaction. Immunologically, depleted Zn²⁺ level might shift the Th1/Th2 balance to Th2 predominance resulting in increased IL-6 generation of COVID-19 subjects [106]. In this connection, decreased blood Zn²⁺ level had been associated with AD. Cognitive impairment associated with olfactory dysfunction had become a common marker of AD and COVID-19[107].

Sex

Males were shown to be considerably more susceptible to COVID-19 mortality than females. Increased ACE2, the impact of testosterone on ACE2, an imbalance between ACE2 products (Ang 1-7, Ang 1-9), and a severe cytokine storm are a few potential causes that may affect males more than women [108]. Therefore, it would appear appropriate to manipulate ACE2 expression using sex hormone modulators to treat COVID-19. On the other hand, it had been discovered that levels of estrogen and testosterone were amyloid beta-clearing and neuroprotective agents [109]. The brain levels of androgen and estrogen in female AD people aged than 80 years were found to be lower than those of age-matched non-AD individuals [110]. Age-related declines in androgen and testosterone levels were seen in male patients who were healthy and AD.

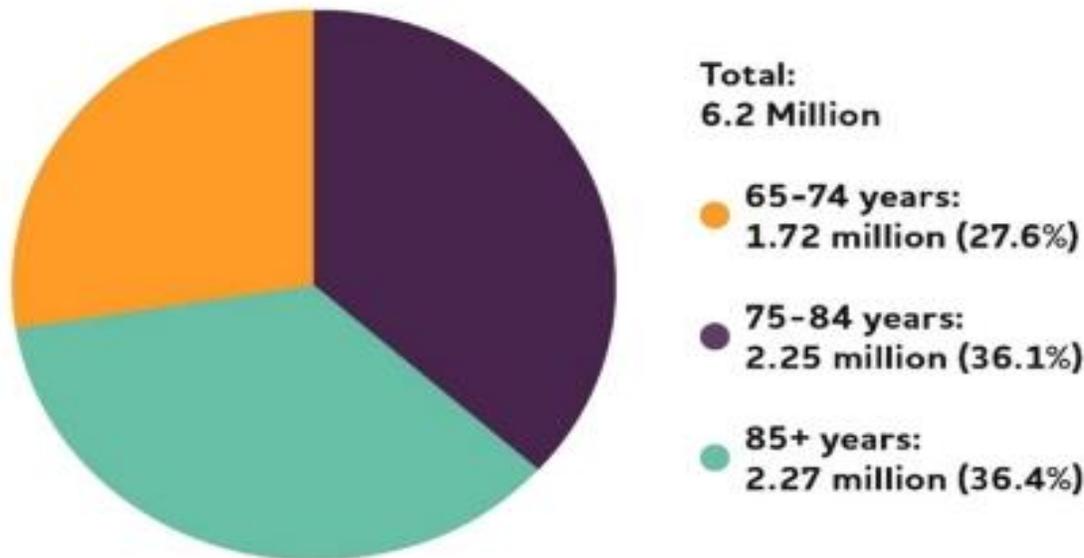


Two pathological characteristics of AD a diagram showing how the pathogenic alterations in AD brains differ from those in healthy brains. On a macroscopic anatomical level, neuronal loss-induced brain shrinkage is discernible. On a microscopic level, toxic amyloid-accumulation, intraneuronal neurofibrillary tangle development, synaptic loss, increased activity of microglia, astrogliosis, excessive cytokine production, and dystrophy of neurites are seen.

post-mortem analysis of a small portion of the typical pathogenic features is explained the prevalence of AD & dementia in the general population [111]. Additionally, no therapeutic trials have so far been effective using A or NFT targeting methods. Therefore, Alternative theories may be used to explain the pathogenic and aid in the creation of creative interventional techniques.

Age-

Both AD and COVID-19 are more likely to affect older adults [112]. Further ageing, however, is not a factor for COVID-19 in individuals above the age of 80, but rather for AD or dementia. Reduction in the susceptibility to subsequent lung inflammation may be the reason, even though the precise process is yet unclear [112-113]. However, AD susceptibility often starts at or after the age of 60, and as people age, the rate of AD pathogenesis increases [113]. Age-related AD pathogenesis has been linked to increased production of reactive oxygen species (ROS), worsened amyloid beta formation, aggregation, and neurodegeneration, disturbed proteostasis, cardiovascular problems (CVD), diabetes, hypertension, and lifestyle modifications [113].



Number and ages of people 65 or older with

Alzheimer's dementia, 2021. Created from data from Rajan et al.

Percentages do not total 100 due to rounding.

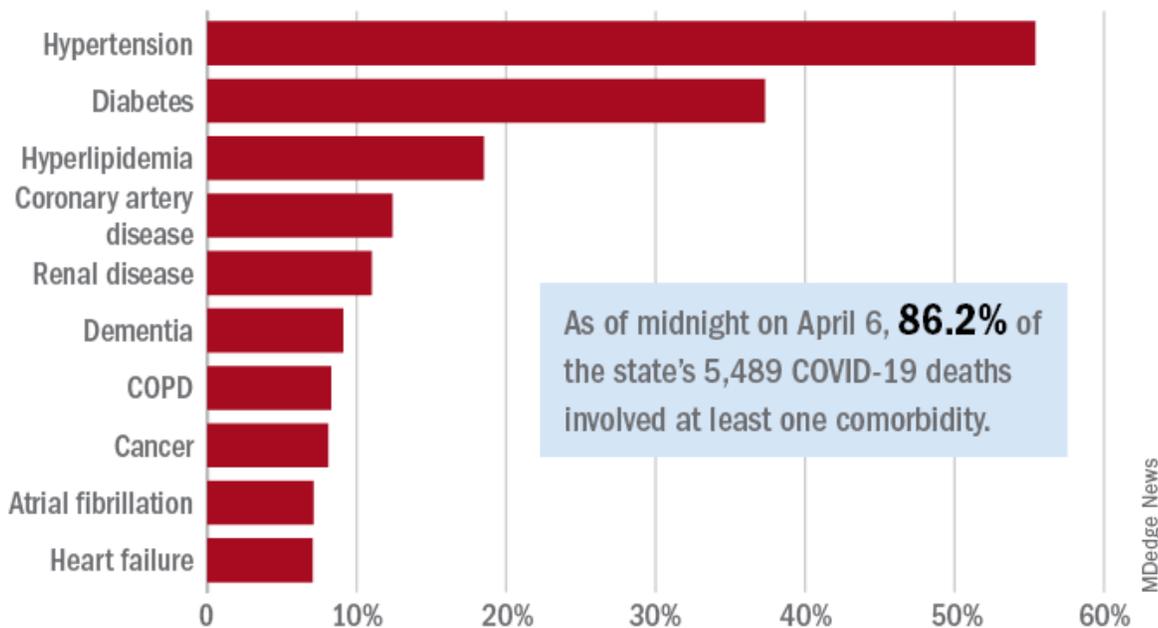
Of the total U.S. population: More than 1 in 9 people (11.3%) age 65 and older has Alzheimer's dementia [114] · The percentage of people with Alzheimer's dementia increases with age: 5.3% of people age 65 to 74, 13.8% of people age 75 to 84, and 34.6% of people age 85 and older have Alzheimer's dementia [115] People younger than 65 can also develop Alzheimer's dementia, but it is much less common and prevalence is uncertain. The Chicago Health and Aging Project (CHAP), a population-based study of chronic diseases affecting older people, and the most recent data from the 2020 projections from the U.S. Census Bureau were used in an updated study to estimate the number of people age 65 and older with Alzheimer's dementia [116]. Although CHAP does not provide national estimates of the prevalence of all dementias, other population-based studies such as the Aging, Demographics and Memory Study (ADAMS), which includes an elderly population that is typical of the country as a whole, do. [117-118]. According to statistics from ADAMS, 11% of Americans 65 and older have dementia [118].

AD patients exhibit elevated morbidity and mortality of COVID-19-

In New York state, just over 86% of reported COVID-19 deaths involved at least one comorbidity, according to the state's department of health. As of midnight on April 6, there had been 5,489 fatalities caused by COVID-19 in the state, of which 86.2% (4,732) had at least one underlying condition, the New York State Department of Health reported April 7 on its tracker. The leading comorbidity, seen in 55.4% of all deaths, was hypertension. In comparison, a recent estimate from the U.S. Department of Health & Human Services put the prevalence of high blood pressure at about 45% in the overall adult population. In New York, the rest of the 10 most common comorbidities in COVID-19 fatalities were diabetes (37.3%), hyperlipidemia (18.5%), coronary artery disease (12.4%), renal disease (11.0%), dementia (9.1%), chronic

obstructive pulmonary disease (8.3%), cancer (8.1%), atrial fibrillation (7.1%), and heart failure (7.1%), the NYSDOH said.

Leading comorbidities among COVID-19 deaths in New York

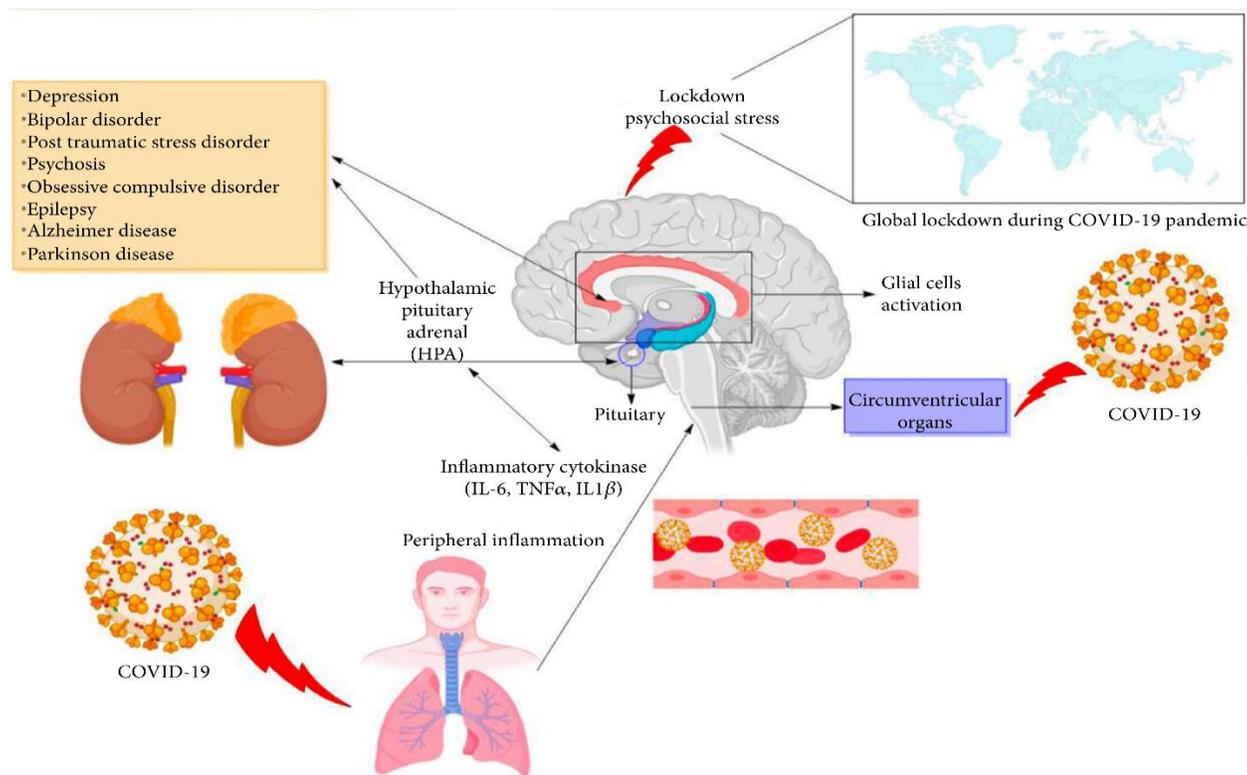


Note: Data reported on a daily basis by hospitals, nursing homes, and other health care facilities.

Source: New York State Department of Health

Other effects of Covid-19 in relation to Alzheimer Diseases -

Ageing and dementia are two important risk factors for Alzheimer in COVID-19-infected people. Second, mental health is weakened, as a result of isolation brought on by psychological or social distance, which can lead to dementia or other psychological illnesses. [119]. Results from Covino et al. among dementia patients who had COVID-19 infection. Their findings from retrospective study, single-centered, and observational analysis at a COVID-19 referral center in Central Italy shows that the probability of mortality is independent of age [120]. On the other hand, acute dementia itself may be a significant risk factor for these people. Based on these data, Bianchetti et al. identified the clinical representation, prevalence, and outcomes of dementia patients among patients who were hospitalized with a COVID-19 disease. Retrospective analysis of data from 627 patients admitted to the acute care hospital in the northern Italian region of Brescia was done. Dementia patients have a significant death rate of up to 40 percent of the total compared to those without dementia [121]. Combining this research on dementia, particularly with the disease's late onset, may greatly increase the likelihood of corona patients dying due to neurological impairment and a high prevalence of neuropsychiatric symptoms, is more susceptible in AD patients.



This has been demonstrated particularly, during the SARS-CoV-2 infectious disease outbreak's compassionate phase. Throughout the infection, psychiatric symptoms may be present in around 80% of AD patients. Despite the possibility of early indications of prodromal phases, these elements are malleable and seem to progress more rapidly in AD. Anxiety, despair, agitation, and growing apathy are among the neuropsychiatric signs of AD that are frequently damaging [122]. But it's also thought to be a result of things like an accelerated pace of AD progression, altered meditative responses, and a decline in the patients' quality of life. Boutoleau-Bretonniere et al. initially presented proof of the effect of custody on the neuropsychological manifestation in AD patients during the COVID-19 epidemic. According to the findings, only 30 percent of the surveyed of AD patients showed neuropsychiatric changes while they were imprisoned. Their caretaker's illnesses and the intensity of their symptoms are strongly correlated with the confinement duration. In contrast to persons with more preserved cognition, AD patients may have worsening neuropsychiatric symptoms, as a result of the constraints [123]. During the total lockdown that occurred during the COVID pandemic, other authors found that the magnitude of neuropsychiatric symptoms of agitation and decreased motor function was the most impacted indicator among AD and MCI [124-125]. While they especially reported tiredness and diarrhea, the common signs of patients with AD with COVID-19 infection, such as breathlessness, fever, and cough, were less common. Finally, although it is necessary for cognitive support and treatment, delirium can result in hypoxia, a characteristic of COVID-19 disease and it can worsen the portrayal of dementia. However, these studies can support the projected danger across the medical spectrum, particularly the neuropsychiatric symptoms during the AD epidemic [126].

1. Impact of covid19 on blood brain barrier permeability-

Microvascular endothelial cells create the blood brain barrier, which shields the central nervous system (CNS) from harmful or heterogeneous microorganisms found in the blood [127]. Tight junctions are crucial to the blood barrier. Zika, Arbo, and west Nile viruses are only a few of the viruses that can damage the blood-brain barrier [128-129]. In vitro and in vivo effects on the blood brain barrier have been used in a number of clinical research. [130]. Through hepatotropic rodent hepatitis type-3 virus, Bleau et al. stimulated corona virus activity in the central nervous system. Type-3 infections cause an increase in the blood-brain barrier permeability and brain invasion. Zonula occludens protein-1 or VE cadherin expression-1 will be induced as a result [131]. According to studies, coronavirus genetic material and viral

particles have been found in brain tissue. area of the cortex and hypothalamus, as well as neuronal cytoplasm [132]. The blood-brain barrier's basement membrane can also be damaged by SARS covid 2[133]. By adsorptive transcytosis, the s1 subunit "spike protein" can pass the blood-brain barrier. The lungs' uptake is likewise influenced by ACE-2 [134]. It also contributes significantly to cellular stress linked to cytotoxicity, which results in the death of cells or induces apoptosis [135]. Therefore, endothelial cell activation results in an inflammatory response and also increases the production of proteases. Which causes protein breakdown by enhancing matrix metalloproteinase [136]. Increased IFN-1 labelling in Covid 19 patients prevent the virus from replicating. They will also increase the production of cytokines, immune active cells (monocytes, macrophages, and neutrophils), and interferon-stimulated genes [137]. increases the production of cytokines, chemokines, and interleukin-1 receptor antagonist (IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IFN, IFN-, and TNF) [138]. A pathogenic inflammatory response is induced by the storm of cytokines that stimulates platelets, neutrophils, macrophages, and monocytes. In a histological study of the brain, CD3+T cells, monocytes/macrophages, and 1 and 2 integrins are discovered in SARS COV-condition.

Future Neurodegeneration Causing Factor-

The brain's cortex and substantia nigra are very susceptible to HCoV invasion through the ACE2 receptor. Coronaviruses are predicted by Lippi et al. to have a significant impact on the genesis of neurological diseases like Parkinson's disease [139]. (PD). According to certain reports, coronaviruses have the ability to increase levels of -alpha synuclein, a crucial Lewy body protein that fosters neurodegeneration. It precisely achieves effective homeostasis by activating stress-induced pathways that target neurodegeneration. There is evidence that alpha-synuclein production may result from H1N1 disease of dopamine neurons cells. As a result, in vitro models that detect the initiating abnormalities in proteostasis may allow dangerous impermeable proteins to persist These results indicate that coronavirus disease can alter Parkinson's disease neurodegeneration by causing an acceleration of the ageing process in brain tissues [140].

The Effect of Coronavirus-

SARS-CoV-2 has been found in brain autopsy and isolated from individuals with COVID-19 infection's cerebrospinal fluid [141-142]. There are now at least two established facts concerning the relationship between neurodegenerative disease and COVID-19, specifically for Parkinson's disease (PD). On the one hand, individuals with PD who have already experienced PD produce antibodies for HCoV in their cerebral fluid [143]. if the virus reaches the brain through the nasal canal, it may result in anosmia and hyposmia [144]. They assert that the olfactory area is the site of the pathogenic aggregation of alpha-synuclein and that hyposmia is a defining premotor PD symptom. Several studies have also shown that viruses can live longer duration in neurons and target them for longer periods of time [145].

Changes to Neurological Disease and Treatment Strategies-

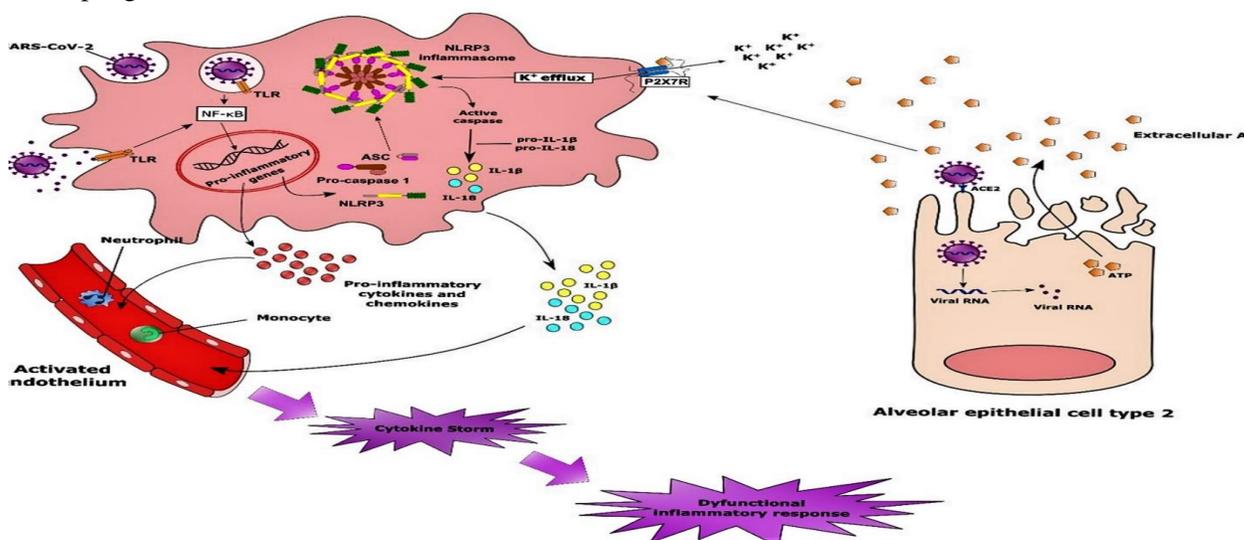
According to Donadio and colleagues, in case-control studies they revealed, the effects of symptomatic SARS-CoV infections on the motor or non-motor neurons as a result, 141 persons with pre-existing Parkinson's disease (PD) who had illness durations that were comparable to controls [146]. When COVID-19 infection is present in PD patients, tiredness is frequently described as the predominate non-motor symptom [147]. Comparatively, cognitive qualities were significantly enhanced; as a result, none of them suffered from autonomic impairment. Patients with PD may have medical disruption. In one-third of the instances, therapeutic changes are necessary, which can be explained by infection-based processes and outdated dopaminergic treatment pharmacokinetics [148]. Due to the unintended consequence of the longer exposure period under lockdown, which causes self-isolation, elevated anxiety, and stress that should be taken into account, the SARS-CoV-2 transmission in patients with pd cannot be restricted to motor symptoms. Anxiety levels among PD patients were compared to those of caregivers and well-known people in recent cross-sectional, case-control research conducted in Iran. An investigation into the prevalence of anxiety among PD patients and their caregivers was conducted [149]. Through vascular injury, systemic inflammation, and direct neuroinvasion, the COVID-19 infection may have an impact on the brain. Due to microglial, T cell infiltration, and consequent neurodegeneration brought on by α -synuclein overexpression, these alterations may culminate in the development of acute Parkinsonism. Due to persistent chronic inflammation and α -synuclein aggregation, COVID-19 may possibly increase the long-term risk of developing Parkinson's disease (PD) in addition to the onset of acute Parkinsonism [150].

Others Neurodegeneration's Causing Factor-

HCoV and its effects on the brain have a long history of correlation, but this relationship is not fully understood; understanding this relationship will be important for future study on AD. Chronic effects following COVID-19 infection, which are frequently associated with a cytokine storm of various inflammatory responses, result in an increase in proinflammatory (IL-1 and IL-6) [151]. Amyloid can cause a perfect storm in AD patients because it enhances the IFN response [152]. IFNs have a significant role in the pathophysiology of AD, showing that amyloid fibril-containing nucleic acids stimulate the expression of IFN-producing genes. IFN, which is linked to amyloid plaques, activates microglia, inducing a proinflammatory response. IFN further triggers the complement cascade, which results in the degradation of synapses. It clarifies one of the issues raised by Presymptomatic AD sufferers who may observe the symptom stimulation brought on by systemic inflammatory reactions brought on by viral infection. Additionally, a few of experts have thought that after recovering from a main SARS-CoV-2 infection, infected individuals may be at a high risk of having impaired cognition. Additionally, to accelerating a neurodegenerative disorder's onset and de novo stimulation, the disease may have a direct unfavorable influence on immune function. They may lead to chance of developing neurological symptoms, which are shown by asymptomatic COVID-19 disease in the brain, according to the data put out.

Potential functions for P2X7 receptors in COVID-19 processes-

The P2X7 receptor is extensively distributed throughout the body [153-154] including in immunological lung and CNS cells, including microglia and oligodendrocytes [155-156]. However, the expression of the P2X7 receptor in neuron and astrocytes is still unknown [157-158]. The Inflammasome reaction to COVID-19 infection may cause the release of ATP during the duration of the infection following virus spike associated proteins only with virus entrance receptor ACE2, as a result of elevated levels of Ang II seen in infected individuals, and in reactions to stimulated ComC mediators [159]. As a result, P2X7 receptors are stimulated, causing an increase in inflammatory reactions as well as a modulation of the BBB permeability and RAAS-related pathways. The P2X7 receptor, a trimeric ionotropic binding site that is a member of both the P2X group of purinergic ligands, has a low selectivity for ATP (EC₅₀ ranges from 0.3 to 1.8 mM) and can generate holes that enable the entrance of massive hydrophilic molecules when stimulated for an extended period of time. Rapid K⁺ efflux, Ca²⁺ influx, and Na⁺ inflow is caused by P2X7 receptor activation. These events stimulate a number of intracellular mediators, including PLA₂, PLC, PKC, PI3K, MAPK, ERK1/2, and p38, among several others [160]. As a result, activation of the P2X7 receptor is linked to a variety of cellular processes, including blebbing of the plasma membrane, exposure of phosphatidylserine in the membrane, production of ROS, interleukin release, cell death, and proliferating [161]. In these conditions, ATP could function as DAMP, which stimulates the nuclear NF- κ B transcription factor and causes the production of pro-IL-1 and pro-IL-18 as well as the NLRP3 protein to be upregulated [162]. Additionally, K⁺ efflux is triggered by P2X7 receptor activation, and this signal is necessary for effective Inflammasome stimulation [163]. Caspase-1 is thus activated, IL-1 and IL-18 mature, and pro-inflammatory cytokines are released [164]. The NLRP3 inflammasome is significantly activated by the P2X7 receptor in a variety of cell types, particularly macrophage and microglia.



Alveolar macrophages may have had a role in the inflammatory process brought on by SARS-CoV-2 infection. Rapid infection of vulnerable cells can induce the release of internal contents, which can result in a long-lasting inflammatory response. extracellular fluid buildup the production of inflammatory genes, even those linked to the NLRP3 inflammasome, is triggered by ATP concentrations high enough to activate the P2X7R involved with the identification of viral products. K⁺ efflux caused by P2X7R activation in alveolar macrophages serves as a strong signal to assemble the NLRP3 inflammasome. Caspase-1 is activated as a result of the creation of this multiprotein complex, and it then cleaves pro-IL-1 & IL-18 into their biologically active versions. In contrast, active caspase-1 may also cleave the gasdermin D protein, resulting in pyro ptosis. The endothelium is activated and additional inflammatory cells, like neutrophils and monocytes, are infiltrated as a result of the release of IL-1 and other chemokines and cytokines from activated macrophages, which will further amplify the inflammatory response. Additionally, activation of the P2X7 receptor encourages the production of other inflammatory cytokines such IL-6, TNF, and CXCL2 CCL2, CCL3. [165-166]. Patients with SARS-CoV-2 infection had higher levels of IL-10, IL-1, INF-, CCL2, TNF-, CXCL10, CCL7, IL-1 blocker, and IL-2 receptor, which are thought to be related to the severity of the disease. P2X7 receptor activation may have contributed to the cytokine storm seen in COVID-19 by triggering the Inflammasome, overswinging inflammatory response with wide - ranging cytokine release, interfering with coagulation, causing diffuse lung oedema, and allowing immune cells as well as inflammatory mediators to infiltrate as explained by Di Virgilio et al. Numerous processes connected to lung dysfunction, as shown in COVID-19 individuals, are controlled by P2X7 receptors [167]. The large ATP release that occurs after the invasion of lung mononuclear phagocytes by SARS-CoV-2 can stimulate P2X7 receptors on macrophages and antigen-presenting cells, raising cytokine, chemokine, and ATP levels. The invasion of inflammatory cells, inflammatory cytokines, apoptosis, and fibrosis were also decreased in P2X7 receptor deletion mice subjected to a lung fibrosis model, whereas P2X7 receptor agonists exacerbated these harmful processes [168,169]. As a result, it is summarized that the cytokine storm and related brain and lung inflammation brought on by Spanish flu infection include P2X7 receptor activation.

Clinical Trial Monitoring for COVID-19 patient Associated with Parkinson's and Alzheimer's –

Many studies are being done on the clinical characteristics of COVID-infected individuals. According to the WHO 550 million reported cases of COVID-19 worldwide, with 6.3 million fatalities [170]. 12,130,881,147 vaccination doses have been given as of July 11, 2022. Examining the risk factors associated with COVID-19 infection and patient fatalities is critical. Uncertainty persists on the primary mechanisms behind the increased transmission rate and degree of illness. In addition to the virus, the patients have various medical disorders such diabetes, cardiovascular disease, and respiratory diseases. Elderly individuals are particularly vulnerable to the virus. A significant risk indicator for the SARSCoVs-2 death rate is believed to be age. The most common characteristic of neurodegenerative disorders in older adults is age. Therefore, it is important to examine Parkinson's and Alzheimer's disease in SARS-CoV-2 infections in older person [171]. Older people with illnesses and neurological disorders including Parkinson's disease (PD) and Alzheimer's disease are at risk from SARS-CoV-2 (AD). There is no conclusive data at this time to support the elevated incidence Parkinson diseases. Additionally, during the pandemic, significant PD symptoms linked to anxiety are frequently observed. A significant mortality rate (40–50%) is observed in PD patients, particularly in those who undergoes advanced treatment. [96]. The most common characteristic of neurodegenerative disorders in older adults is age. Therefore, it is important to examine Parkinson's and Alzheimer's disease. Older people with illnesses and neurological disorders including Parkinson's disease (PD) and Alzheimer's disease are at risk from SARS-CoV-2 (AD). Additionally, during the pandemic, significant PD symptoms linked to anxiety are frequently observed. A significant mortality rate (40–50%) is observed in PD patients, particularly in those who undergo extensive medication [172]. Although there is no evidence to substantiate the relationship between neurodegenerative disorders and COVID-19 individuals, it is being looked at globally as a prospective investigation of the clinical treatment approach for ND patients hospitalized. There are no current clinical guidelines. Therefore, an attempt should be made to ensure PD and AD patients continue to receive anti-PD and anti-AD therapy.

An equal levodopa dosage is important in PD therapy medications to prevent respiratory difficulties and muscular bradykinin stiffness brought on by dopaminergic depletion. If already being used on patients, apomorphine pump treatment and carbidopa intestinal gel treatment should be continued. When oral drug delivery is no longer feasible, as in severe kinetic patients with dysplasia symptoms, PD medicines may need to be modified in hospitals [173]. Memantine and cholinesterase inhibitors (ChEIs) such as donepezil, rivastigmine, and galantamine are used to treat AD. Additionally, antipsychotics and antidepressants are used to treat patients' behavioral and mental health issues (2). Even though donepezil and galantamine have limited pharmacokinetic drug interactions, cytochrome P450 (CYP450) enzymes. Galantamine and donepezil's pharmacological effects might become more pronounced while receiving CQ/HCQ therapy [174]

Effects of the COVID-19 Pandemic on Aging-Related Neuroinflammation in Parkinson's and Alzheimer's Disease.

The olfactory nerve, which is present in both humans and animals, can allow SARS-CoV-2 to enter the brain without any early respiratory involvement [175]. Infection of COVID-19 happens when virus glycoprotein spikes attach to ACE2 receptors. The dopamine neurons in the striatum and the cardiorespiratory areas of the medulla are two examples of the different ACE receptors found in the human brain [176]. SARS-CoV-2 infection is nonetheless associated with mobility impairment, particularly for PD. The second piece of evidence, which demonstrates how coronavirus penetrates the nasal channel before moving to the brain and causing anosmia or hyposmia. According to accounts, hyposmia is a frequent premotor feature of PD. The olfactory region is the ideal site for the pathogenic accumulation of alpha-synuclein, which may not simply be fate.

Parkinson's and Alzheimer's Disease Relationship between SARS-CoV-2 and Glial Cells-

The substantial involvement of glial cells in controlling brain homeostasis and viral infection predicts that downregulated glial cell activity may have an impact on COVID-19 development both overtly and implicitly. In settings of neuropsychiatric and neurodegenerative illness, the glial cells (microglial and astrocytes) are crucial for preserving brain homeostasis and CNS responsiveness. These diseases frequently point to a common neuroinflammatory demand that the activated glial cells recognize and respond to by producing inflammatory and anti-inflammatory cytokines, proinflammatory chemokines, free radicals, and neurotrophic factors. The evidence implies that astrocytes and microglia are predicted to have a major impact on brain function during a virus, including in COVID-19 patients, due to a vast number of activities performed by glial cells in the neuro - inflammatory processes. Astrocytes and microglia exhibit the age-based remodeling process, which may ultimately result in harmed functional properties and aid in the emergence of neuronal disorder[177]. Similar to this, glial cells are seen in the older brain in a variety of functional and morphological problems, including increased ROS, reduced phagocytic activity and fatality, inflammatory cytokines production, and increased DNA mitochondrial damage. Because of this, it is not observed in older COVID-19 patients. These alterations may lead to the impairment of the typical glial cell neuroprotective activity and generate neuroprotective and neurodegenerative illness. It is generally established that COVID-19 infection patients may have worsened reported defects and neurological damage due to inadequate proinflammatory cytokine production; however, it is unknown whether microglia activation is advantageous or detrimental to COVID-19 patients' brains.

Conclusion-

The new coronavirus infection has had an unparalleled impact on the global healthcare system. The sustainability and quality of the ongoing and upcoming AD and PD studies have also been threatened by this epidemic. Local effects, however, will fluctuate and become more unique dependent on specific elements including incidence, cases of related deaths, the availability of resources, and societal changes that may influence the COVID-19 pandemic. Simple generic suggestion is ineffective due to these local changes brought on by AD and PD heterogeneity. Therefore, a person's awareness of their likely effects and approach to reducing them may help to lessen the negative effects they have on AD, PD, as well as the people who care for them. Additionally, more investigation is required to show the precise mechanism by which HCoV infection results in neuronal damage, especially if HCoV may really utilize the linked routes of CNS invasion. In that situation, it may be rather intriguing to examine how certain systems interact with the particular symptoms of neurological diseases; this issue has not yet been resolved.

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