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Impact of Covid-19 on Alzheimer Patients: How One Crisis Worsens the Other

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Abstract

The coronavirus has caused chaos in the lives of many people in our society, one of which is the disruption of our daily routines. For those with Alzheimer's disease or those who care for someone with Alzheimer's disease, the coronavirus has the potential to be lethal. The COVID-19 epidemic has wreaked havoc on people with Alzheimer's disease (AD) and other dementias. Corona virus illness, which is characterised by severe acute respiratory syndrome, has arisen as a substantial comorbidity. The immediate physical effects of Covid-19 have been widely investigated, but little is known regarding the long-term consequences. The authors investigate the symptoms of Alzheimer's disease and how it worsens COVID-19, as well as the mechanisms at work at all levels, from biological to social. COVID-19's impact on brain function and viral entry pathways into the brain, as well as the factors that lead to COVID-19-related cognitive impairment, were also examined. The researchers looked on the prevalence and mortality of COVID-19 in Alzheimer's patients, as well as the impact of the pandemic on uninfected dementia patients and Alzheimer's disease management.

Keywords COVID-19; Alzheimer Patients.

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Introduction

Data on the clinical features of people sick was being questioned as of December 2019, when the coronavirus disease 2019 (Covid-19) initially surfaced in Wuhan and swiftly spread across China. The coronavirus-2, which causes severe acute respiratory sickness, produces COVID-19, a global public health threat (1). Fever, colds, throat pains, coughing, shortness of breath, and other respiratory symptoms are caused by SARS-CoV-2, which predominantly affects humans' respiratory systems. Some unusual respiratory symptoms include migraine, dizziness, autonomic dysfunction, stroke, and loss of consciousness, memory, and recall. According to current research, SARS-CoV-2 can infect and target the central nervous system. Furthermore, neurological abnormalities were seen in more than one-third of COVID-19 individuals with symptoms (3).

The COVID-19 epidemic is causing massive illness and death all across the planet. Older people die at a five-fold greater rate than the general population, (4) putting a strain on health-care systems and generating societal disturbance, as well as putting individuals with Alzheimer's disease and related dementias (ADRD) in severe danger (5). COVID-19 has a deleterious influence on the brain by reducing awareness levels (6). COVID-19 infections are especially dangerous for Alzheimer's patients because they are more prone to forget or misinterpret basic public health guidelines. Physical separation is also not an option for people who rely on others to do daily tasks and satisfy basic needs, especially those with severe dementia symptoms and major physical limitations (7). In addition, older persons with dementia had a greater rate of COVID-19 infection and a higher risk of COVID-19 infection-related mortality. As a result, in order to recuperate from their diseases or protect themselves from infection, these patients must suffer lengthy lockdown periods. Longer lockdown times are linked to more severe neuropsychiatric symptoms and a higher level of behavioural abnormalities (8). COVID-19 patients with neurological symptoms are more likely to have blood markers that suggest brain injury, neuroinflammation, and Alzheimer's disease. Individuals who have cognitive decline after COVID-19 are more likely to have low blood oxygen levels after short bouts of physical exertion and to be in poor physical condition overall. Dementia is one of the most prevalent COVID-19 Neurological sequelae. The most prevalent cause of dementia is Alzheimer's disease. It is a neurological disorder. The brains of Alzheimer's patients generate beta-amyloid (A) or neurofibrillary tangles, which impair learning and memory (NFT). Patients with Alzheimer's disease, whose symptoms range from mild to severe, are completely reliant on their caregivers (9,10). Caregivers' expectations for Alzheimer's disease management clash with COVID-19's since COVID-19 is extremely infectious and demands seclusion and quarantine. COVID-19 makes it more difficult to cope for Alzheimer's patients, carers, families, the community, and industry.

Identifying shared etiological elements might aid future COVID-19 and Alzheimer's disease treatment and management. This study investigates the links between COVID-19 and Alzheimer's disease (AD), as well as existing challenges and future aspirations for improved Alzheimer's treatment choices, in the context of the COVID-19 issue.

COVID-19: Symptoms and Epidemiology

Coronaviruses have been associated to mild to severe respiratory diseases for more than 50 years (11). Despite the fact that coronaviruses have been found in a wide range of mammals, bats are thought to be an essential major reservoir for coronaviruses (12, 13).

The common cold is caused by the human coronaviruses 229E, HKU1, NL63, and OC43 (6). When two newly identified coronaviruses, SARS CoV (2002) and MERS-CoV (2012), produced severe acute respiratory infections and enterococci outbreaks, all prior approaches to dealing with this virus group were drastically altered. At the end of 2019, a novel coronavirus, presently known as SARS-CoV-2 (2019), was found in Wuhan, China.

The World Health Organization classified the outbreak a public health danger of global concern on January 31, 2020. On April 16, 2020, COVID-19, a new coronavirus outbreak, swept the world, inflicting 2 million sickness and 137 thousand fatalities. Because of their ubiquity, we should pay more attention to coronavirus infection treatment and prevention than we did in the past.

The number of patients, even mild cases, must be tallied to adequately measure the pandemic response. The prevailing notion is that the sickest persons should seek medical help and be evaluated; case adverse event and hospitalisation ratios are routinely used to estimate the damage early in an epidemic. Because it takes time for cases to advance to severity or infected individuals to die, and the number of sick people may not be exactly estimated, these figures should be used with caution (14). The early cases of Covid-19 reported in China were big enough to warrant medical attention and testing, as with previous epidemics, although the precise number of persons infected is unclear. The death rate

among medically attended people is thought to be about one in ten.

Simple numbers of reported cases may be unreliable predictors of the epidemic's progression if access to treatment or lab testing is limited, or only those with severe symptoms are checked. During the 2009 influenza pandemic, a mechanism for maintaining monitoring when the patient population became too vast to count was revealed. This method, which can be used to test Covid-19, assists in determining the number of people who have a highly sensitive but non-specific syndrome (for example, respiratory distress infection) each week and testing a subset of these people for novel coronaviruses using existing monitoring systems or survey design. The caseload is derived by multiplying the incidence of respiratory ailments (for example) by the proportion of positive cases in a certain jurisdiction (15). The time has come to put in place the infrastructure required for such monitoring. This and other public health investigations, such as virus testing, can benefit from electronic laboratory reporting.It's beneficial to combine data from parallel surveillance studies, epidemiological field research, and clinical trials (14). Observational studies in safe environments, such as schools, workplaces, or communities (community surveys), can help describe the overall burden as well as neighbourhood and household attack rates; perhaps more importantly, they can allow for the rapid detection and evaluation of the pandemic by counting the range of ailments, hospitalizations, and mortalities in a well-defined population and attempting to extrapolate that rate to the larger population (16). Understanding transmissibility is critical for projecting epidemic spread and the potential for long-term transmission. Several researchers have used epidemic curves to estimate the breeding amount R0 of SARS-basic CoV-2; however, household investigations can give better data on transmission duration and likelihood, which might help determine R0 (17)

Domestic studies can also help define the role of subclinical, asymptomatic, and mild infections in transmission, allowing evidence-based decisions to be made about which management initiatives to prioritise. If symptomatic people are the primary source of communication, measures based on identifying and isolating them will be far more effective. If those who aren't sick may spread the illness, community isolation measures like closing schools and prohibiting public meetings should be prioritised. To determine if school closures pose a substantial risk to children's health, education, and productivity, as well as whether working parents are obligated to care for their children, we must first determine whether children are a large source of pollution. Household surveys may also be used to conduct viral dropping studies, which can help forecast when patients are infectious and how long they should be separated.

One of the recommendations' main themes is that viral testing should not be confined to therapeutic therapy. A part of the testing equipment must be set aside to aid public health specialists in identifying the progression of the disease and the severity of the illness. Despite the fact that this approach is likely to provide a high number of negative test results, it will provide a far better knowledge of the epidemic's progression and a more effective use of resources to combat it. Testing in unexplained clusters or severe instances of acute respiratory infections, independent of a patient's travel history, might be a sensitive technique for locating lost transmission channels. Such findings are especially noteworthy in view of recent evidence that Singapore, which has one of the world's best public health systems, has uncovered cases that have yet to be connected to confirmed cases of China travel. It seems to reason that if such inconspicuous introductions happen in Singapore, they happen everywhere.

Early attempts to characterise SARS-CoV-2 will pay huge dividends in terms of pandemic preparation. Assume, as many experts do, that persistent transmission extends beyond China's borders. In such cases, the urgency of the epidemic will need decisions on which therapies to deploy, when to deploy them, and for how long to deploy them.

Starting these epidemiology and surveillance activities as soon as possible allows us to discover the most effective pandemic control methods while avoiding steps that are either excessively costly or substantially restrict frequent travel.

Severe occurrences have already swamped or will shortly inundate several Chinese cities. Many of them may find it challenging to do the types of research described here. Systematic surveys of people who aren't known to have Covid-19 or who have a minor respiratory infection are an exception, since they're used to determine if they're presently subclinically ill, have been infected before (through serologic testing), or both. These investigations, which will aid in determining the severity spectrum, will be particularly useful in areas where the most incidents occur.

Fortunately, the number of cases discovered outside of China is still manageable for public health officials - and much too tiny to merit further investigation. However, as the number of occurrences increases, authorities outside of

China must be prepared to investigate. According to the study, the most common coronavirus symptoms are fever (81.2 percent), cough (58.5 percent), weariness (38.5 percent), dyspnea (26.1 percent), and the presence of sputum (25.8 percent) (18).

The early indications of COVID-19 were detailed in this Systematic Review and Meta-Analysis Study. The pathophysiology of the 2019-nCoV virus is similar to that of the two previous pandemic viruses, which occurred in 2003 and 2012 (SARS-CoV and MERS-CoV, respectively). Cytokines may have a role in the spread of the human coronavirus. According to indirect evidence, severe fever, pneumonia, and hypoxemia occur in phase 2 of 2019-nCoV infection despite a significant decline in viral load (21). The clinical signs of COVID-19 were investigated in this literature review and conceptual analysis in order to have a better understanding of the condition.

The most prevalent symptoms were fever, cough, and weariness, which were similar to those of a viral illness or pneumonia. Similar to previous investigations, the current study found fever in 81.2 percent of patients, cough in 58.5 percent of cases, and fatigue in 38.5 percent of cases (2) and (22). Fever is the most common symptom among COVID-19 patients, however it does not affect everyone. Fever, like vomiting, is a sign of illness and should be addressed carefully (23) and (24). Fever (temperatures above 39°F) is frequently associated with more serious disease and a longer hospital stay (25-27). COVID-19 generates fevers that are higher than those caused by SARS and MERS (28, 29)

COVID- 19: Pathogenesis

Stage 1: Asymptomatic (during the first 1–2 days after infection)

The SARS-CoV-2 virus enters the nasal cavity and multiplies by adhering to epithelial cells. SARS-CoV2 and SARS-CoV1 both utilise the ACE2 receptor (14). According to in vitro investigations with SARS-CoV, iliated cells are the first cells in the airways to be affected (30). However, a single-cell RNA research reveals that conducting airway cells only express a modest amount of ACE2 and have no obvious cell type preference, indicating that this theory may need to be reconsidered (31). The virus is spreading locally, but there isn't much of an innate immune response. Nasal swabs can be used to identify the virus at this stage. These persons are infectious, even if their virus burden is modest. The results of the viral RNA RT-PCR might be used to predict viral load, future infectivity, and clinical outcome. It's likely that the results of these experiments will lead to the creation of super spreaders. The sample collecting technique must be standardised for the RT-PCR frequency ratio to be valid. Swabs obtained from the nose are more likely than swabs taken from the throat to be responsive.

Stage 2: Response of the upper airway and the conducting airway (Next few days)

As the virus spreads and migrates down the respiratory system, the innate immune response along the conducting airways becomes stronger. The virus and early symptoms of the typical immune response should be included in nasal swabs or sputum. COVID-19 is a clinically evident condition at the moment. In the future, CXCL10 levels might be used to predict clinical outcomes (32). Epithelial cells infected with the virus produce large beta and lambda interferons. CXCL10 is an interferon-responsive gene with a high signal-to-noise ratio in the sensitivity of alveolar type II cells to SARS-CoV and influenza (33). In SARS, CXCL10 was also employed as a disease marker. and (34) (35). Determining the innate immune response of the host may help predict the disease's future course and the need for more stringent care and (32) (36).

The illness will be mild in around 80% of affected people, affecting primarily the upper and conducting airways. These people can be monitored and treated symptomatically at home.

Stage 3: Hypoxia, infiltrates of ground glass, and ARDS development

Unfortunately, about 20% of infected people may develop stage 3 illness, which involves lung infiltrates, and some will have a potentially fatal infection. At initially, the death rate was thought to be approximately 2%. It does, however, change considerably with age (37). Death and morbidity rates may be altered if the prevalence of mild and asymptomatic people is better known. In the lungs' gas exchange units, the virus has now infected type II alveolar cells. SARS-CoV and influenza infect type II cells more frequently than type I cells (38, 39). On the lung's perimeter and subpleural portions, infected pulmonary branches can be seen in large numbers (40, 41). The discharged virus particles infect type II cells in nearby units and form a self-replicating respiratory toxin. In some areas of the lungs, the majority of type II cells should be destroyed, triggering secondary epithelial regeneration pathways (42). In most circumstances, type II cells are the progenitors of type I cells. This predicted sequence of events was demonstrated in a mouse model of influenza pneumonia (43, 44). SARS and COVID-19 produce severe alveolar damage, resulting in fibrin-rich hyaline membranes and a few multinucleated large cells (45, 46). Some kinds of ARDS might result in more severe scarring and fibrosis due to abnormal wound healing. A significant innate and acquired

immune response, as well as epithelial regeneration, will be required for recovery.
Giving epithelial growth factors like KGF, similar to influenza, may damage and increase viral load by increasing the number of ACE2 expressing cells (47). The elderly are particularly susceptible due to reduced immune responses and a restricted ability to mend damaged epithelia. Mucociliary clearance is also reduced in the elderly, making it simpler for the virus to move to the lungs' gas exchange units (48).
Despite the fact that people can test positive for PCR for up to 70 days, a coliform virus is seldom found beyond the 14th day of symptoms (18).The most likely reason of viral replication termination (viral death) is a delayed interferon response in conjunction with the formation of host defence (the production of neutralising antibodies) (49, 50). Immune cell activation must be minimised once virus replication has ceased to prevent the immune system from becoming overactive and inflicting additional tissue harm. The prolonged inflammatory response in people with severe COVID-19 is driven by an overactive immune system rather than a lack of viral clearance. Macrophage transcription activity with powerful cytokine release remains after the virus has been eliminated (51). This might be due to natural killer and cytotoxic T cells being exhausted and unable to eliminate active macrophages (52, 53). A substantial concentration of viral RNA fragments might come from a high viral load. SARS-CoV ssRNA GU rich components, according to Li et al.(54), demonstrated strong immunostimulatory activity, releasing large amounts of proinflammatory cytokines TNF-, IL-6, and IL-12 via TLR7 and TLR8 pathways (55). Patients with severe COVID-19 infection have a progressive pulmonary phase despite viral clearance, which is most likely owing to persistent macrophage activation and proinflammatory mediator generation. When macrophages are infected with SARS-CoV-2, they convert from mitochondrial to cytosolic glycolysis metabolism (56). SARS-CoV-2–infected macrophages produce more cytokines as a result of this oxidative reprogramming, aggravating the hyper-inflammatory state. This is crucial because little changes in lifestyle may be able to reverse metabolic reprogramming (57). The activation of macrophages and monocytes in patients infected with SARS-CoV-2 may be prolonged. Patterson and colleagues observed spike protein-expressing activated monocytes in "long-term patients" up to 15 months after illness (58). Additional difficulties have been discovered after immune profiling of COVID-19 "recovered" patients. Convalescent plasma donors reported decreased CD4+ T and B cells two months after recovery, according to Orologas-Stavrou et al (47, 59). This study discovered that previously hospitalised convalescent plasma donors had low CD8+ regulatory cells and a Th17 profile, indicating a delayed proinflammatory response. These researchers found similar results in a follow-up study eight months after COVID-19 infection (60).
While the pulmonary phase of COVID-19 is caused by a variety of biological pathways and processes, we believe that severe COVID-19 is caused by two basic pathogenetic mechanisms: i) endothelialitis with concomitant immunothrombosis affecting both the lung and brain microcirculation, and ii) an accumulation of microglia in the lung (alveolar macrophage activation syndrome) with the resulting hyper-inflammatory optimal leading to multi-organ failure.
Autopsies, single-cell profiling of bronchoalveolar lavage (BAL) fluid collected from critically ill people, and an assessment of the clinical characteristics of severe COVID-19 all support this theory. As a result, the findings show that severe COVID-19 sickness is caused by an immunopathology unrelated to the virus. Furthermore (49), (61). In addition to the lungs, severe COVID-19 affects the brain, heart, gastrointestinal system, liver, kidneys, and skin (52). A variety of risk assessment methods have been established, enabling for the early detection of COVID-19 patients who are at risk of progressive organ deterioration, ICU admission, and hospital mortality (62).

Alzheimer's disease increases morbidity and mortality (COVID-19)

COVID-19 is linked to an increased risk of morbidity and death in dementia patients.
According to recent studies, Alzheimer's disease is associated with a significant increase in COVID-19 morbidity. According to a Spanish retrospective research, one of the most prevalent comorbidities among dead COVID-19 patients is cognitive impairment (29.1 percent). Furthermore, Alzheimer's disease was the most prevalent cause of cognitive impairment in the COVID-19 group (9.3 percent of all patients) (63). Furthermore, another observational study conducted in Spain revealed that the AD group had a higher COVID-19 infection rate (15.1 percent) (64). According to this study, AD appears to be a substantial COVID-19 comorbidity.
Several studies have established a relationship between Alzheimer's disease and COVID-19 mortality. According to statistics acquired from a tertiary hospital in Spain, patients with cognitive impairment had a shorter survival time following the beginning of symptoms than patients without cognitive impairment. COVID-19 patients with

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AD (54.5%) had significantly higher mortality rates (2 = 4.94, P = 0.045) than COVID-19 patients with FTD, suggesting that COVID-19 severity is linked to the course of AD (65). A Korean team used multivariate logistic analysis to evaluate the contribution of various factors to death rates, including "age, Alzheimer's disease, chronic lung disease, stroke, hypertension, coronary vascular disease, dyslipidaemia, chronic kidney disease, diabetes, and history of taking angiotensin II receptor blockers or ACE inhibitors," and found that only "age, AD, chronic lung disease, stroke, hypertension, coronary vascular disease, dyslipidaemia, chronic kidney disease, diabetes, and history of taking Furthermore, COVID-19 Case Mortality Rates (CMR) data from 93 countries found that asthma had a stronger positive link with CMR than respiratory infections (28) and chronic obstructive pulmonary disease (both of which had a less positive relationship with CMR) (66). Alzheimer's disease is a significant demographic risk factor for COVID-19 death, according to these findings.

The factors that could contribute to Alzheimer's disease-related COVID-19 morbidity and mortality

Age

Advanced age is the most significant risk factor for Alzheimer's disease. Alzheimer's disease (AD) mostly affects those over 65 (about 90% of cases), and its prevalence doubles every 5 years, resulting in a time-dependent exponential increase (67). Growing older is also linked to COVID-19-related disease and mortality (68, 69). COVID-19 patients over the age of 59 had a five-fold greater death rate than those under the age of 59 in Wuhan, China (70). In Italy, the first country to be ravaged by the pandemic after China, the COVID-19 case fatality ratio (CFR) was around twice as high as the total CFR in the 1980s and 1990s (71).

Lack of mental capabilities and personal care

The morbidity of COVID-19 was greater in Alzheimer's patients, which might be attributed to their particular living condition. Patients suffering from Alzheimer's disease are unable to care for themselves and are less aware of changes in their surroundings. As a result, many Alzheimer's patients are admitted to nursing facilities, which have been particularly hard impacted by the COVID-19 epidemic in several countries. Nursing home residents, for example, accounted for 40% of all mortality in the United States during the first wave of the COVID-19 pandemic although being fewer than 1% of the population. SARS-CoV-2 is a respiratory virus that may swiftly spread among people who live in close quarters or work in occupations that demand a lot of interpersonal interaction (72).

Self-protection is also diminished in Alzheimer's disease patients due to a loss of awareness of environmental changes. According to a Japanese research, just 38.2 percent of Alzheimer's sufferers were aware of the COVID-19 pandemic (73). Furthermore, due to cognitive impairment, 74.5 percent of Alzheimer's patients were unable to use face masks appropriately on their own, delaying the diagnosis of the epidemic. Another poll in Japan indicated that just 31% and 24% of Alzheimer's disease patients, respectively, were aware of the COVID-19 epidemic and the necessity to wear a mask (74). In Alzheimer's patients, a lack of knowledge about keeping "social distance" (1.5–2 m) or wearing face masks may increase the risk of SARS-CoV-2 infection. Patients with Alzheimer's disease have difficulty remembering safety precautions.

Direct pathological changes during Alzheimer's

ApoE, the most common risk gene for sporadic Alzheimer's disease, may be connected to SARS-CoV-2 infection (75). In the UK Biobank population cohort, the ApoE e4 allele was found to increase the likelihood of severe SARS-CoV-2 infection. Because the protein products of the ApoE cluster genes have been shown to behave as viral receptors for a variety of viruses, including hepatitis C and herpesvirus, they may also act as SARS-CoV-2 receptors (75). ApoE dysfunction has also been linked to cardiovascular disease and obesity, both of which enhance the chance of developing COVID-19 (76, 77).

The infection of SARS-CoV-2 may be aided by Ca2+ dysregulation in AD. An oligomer attaches to the plasma membrane and forms holes, allowing Ca2+ to flow freely (78). The N-methyl-D-aspartic acid receptor, the -amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid receptor, and the L-type voltage-gated calcium channels are all directly stimulated by an oligomer, resulting in an increase in intracellular Ca2+ (79). Many processes, including NFT production, electrophysiological disturbance, and neuronal death/degeneration, contribute to AD when intracellular Ca2+ levels are extremely high (80). Both SARS-CoV and MERS-CoV require Ca2+ to infect their hosts (81). Furthermore, certain RNA viruses interfere with Ca2+ homeostasis by altering calcium channels and pumps, resulting in host cell death and viral replication (82). Ca2+ dysregulation may enhance viral infection in Alzheimer's brains, despite a scarcity of relevant experimental data. The Ace2 gene, but not the Ace1 gene, was expressed at greater levels in Alzheimer's disease mice brain tissues than in normal samples, according to a genome-wide

association study (83, 84). In the peripheral blood, however, there was no change in Ace2 gene expression levels between healthy and diseased brain regions. Similar patterns have been discovered in human brain tissues. Ace2 expression levels grow in association with the severity of Alzheimer's disease, according to a microarray research (85, 86). In brain tissues from Alzheimer's disease patients with moderate cognitive impairment, Ace1 transcript levels were lower than in healthy donors. Increased ACE2 production in Alzheimer's disease brains might let SARS-CoV-2 enter the central nervous system and disseminate. ACE2 hydrolyzes Ang II to produce Ang-(1–7), which binds to Mas and activates a variety of downstream signalling pathways, including the PI3K/Akt/CREB/BDNF/TrKB pathway (74, 87). While more study is needed, these findings imply that ACE2 may have a role in the treatment of the neurological and mental symptoms of SARS-CoV-2 infection (98). Furthermore, a new study has linked tau hyperphosphorylation, as well as the accumulation of neuronal internal microtubules and A peptides, to a decrease in the activity of the ACE2/Ang(1–7)/Mas axis (99, 100). SARS-CoV-2 may target ACE2 and lower its expression or activity when compared to healthy persons and vascular dementia patients, causing alterations in cognitive function and aggravating cognitive impairment.

Acetylcholine is a neurotransmitter that aids in memory formation. Only in Alzheimer's patients do the activities of choline acetyltransferase, the enzyme responsible for Ach production, deteriorate dramatically, particularly in the temporal lobe (88). When ChAT activity decreases, so does choline absorption and Ach release, leading in severe presynaptic cholinergic dysfunction. Alzheimer's disease affects memory, learning, and sleeping and waking routines (89). An in silico research (90) found that raising prenatal choline levels in the mother's body can protect the baby's developing brain from the negative effects of SARS-CoV-2 infection, showing that Ach is involved in COVID-19-driven inflammation. These findings suggest that a reduction in Ach synthesis in the CNS of Alzheimer's patients may impair a critical anti-inflammatory mechanism, culminating in COVID-19's uncontrolled cytokine storm.

Neuroinflammation is another important pathogenic characteristic of Alzheimer's disease. In Alzheimer's brains, higher amounts of microglial-derived cytokines (e.g., TNF-, IL-1, and IL-6) and other immune mediators have been discovered, indicating a continuous inflammatory state (91). TNF and IL-6 levels in Alzheimer's patients' blood were likewise found to be significantly higher than in healthy donors' blood (105). COVID-19 causes systemic inflammatory responses and, in severe cases, a cytokine storm, as previously documented. Extremely high cytokine levels in patient blood have been connected to COVID-19 mortality (92). COVID-19 patients' plasma proteomes exhibited the most altered cytokines/chemokines, indicating that they might be used as early markers to monitor disease severity. The inflammatory signs of AD and COVID-19, according to this observation, are comparable. Existing inflammation in Alzheimer's patients may boost the generation of pro-inflammatory cytokines after infection with SARS-CoV-2, impairing immune responses and increasing COVID-19 mortality.

Deficiencies in nutrition

An rise in the frequency of Alzheimer's disease patients of varied severity has been connected to malnutrition. More than 95 percent of Alzheimer's patients were malnourished or at danger of malnutrition, according to an Italian research (93). More than one-quarter of COVID-19 patients were at risk of malnutrition, and more than half of COVID-19 patients were malnourished, according to a cross-sectional study in China (94). Malnutrition has been connected to hospital length of stay and fatality rates (95, 96). Diabetes and other comorbidities are more common in COVID-19 individuals who are malnourished or on the verge of starvation. As a result, malnutrition caused by Alzheimer's disease may have a negative influence on the prognosis of COVID-19.

Finally, research suggest that Alzheimer's disease may have played a role in the development of COVID-19. Pathological abnormalities spanning from the molecular to the systemic levels, as well as lifestyle changes, are seen in Alzheimer's disease patients. All of these changes would raise COVID-19 morbidity and mortality by raising the risk of infection, viral infection, deterioration of patient conditions, and death. To improve their health during the COVID-19 crisis, COVID-19 persons with AD will need more intensive care and specialized/personalized therapy procedures.

Drug interactions

Alzheimer's disease is now treated using cholinesterase inhibitors (ChEIs) such as donepezil, rivastigmine, and galantamine (97). Extracts, inhibitors, and inducers can all have an effect on cytochrome P450 (CYP450) enzymes (for example, CYP2D6, CYP3A4) (98). Two possible COVID-19 medicines, chloroquine (CQ) and hydroxychloroquine (HCQ), can be metabolised by CYP2D6 and CYP3A4, respectively, resulting in substantial alterations in the pharmacological effects of ChEIs (99). If

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azithromycin, another potential COVID19-causing medicine, is used to treat Alzheimer's disease, a similar scenario may emerge. Additionally, lopinavir/ritonavir inhibits CYP3A and CYP2D6, activates CYP1A2, CYP2B6, CYP2C19, CYP2C9, and glucuronyl transferase, and inhibits drug transporters such glycoproteins. By elevating ChEI plasma concentrations, lopinavir and ritonavir have the potential to cause toxicity (113). As a result, cardiac adverse effects (such as bradycardia, heart block, and QT interval prolongation) may develop when both ChEIs and CQ/HCQ or azithromycin are given at the same time, increasing the COVID-19 mortality risk (113).

Comorbidities associated with Alzheimer's

Since the single-disease approach may limit therapeutic efficacy due to a lack of consideration for multimorbidity, medical comorbidity in Alzheimer's disease has gotten a lot of attention. Hypertension is the most prevalent comorbidity in Alzheimer's disease (55%) followed by osteoarthritis (38%) depression (32%), diabetes mellitus (26%), and coronary artery disease (26%) (26 percent) (26% of total) (Twenty-six percent of the total) (Two-thirds of a percent.) (100). Furthermore, a research indicated that Alzheimer's disease patients have a substantially greater frequency of diabetes and depression than controls, indicating a link between the illness and these two conditions (94). Diabetes has been related to COVID-19 as a major risk factor (101). Diabetes was shown to be the second most prevalent comorbidity in a retrospective study of COVID-19 patients in China using multi-center cohorts (19 percent) (102). Diabetes was found to be a comorbidity in 31% of those who died. Diabetes was linked to a considerably higher risk of COVID-19 mortality in a whole-population research done in England (103). Diabetes has been linked to an increased risk of mortality from cardiovascular events, thrombosis, and DIC in COVID-19 hospital patients (119). COVID-19 and Alzheimer's disease are linked to high blood pressure and coronary heart disease (100,102). Doctors frequently misdiagnose various diseases in Alzheimer's disease patients due to their inability to verbalise or recall particular concerns or consent to full diagnostic tests, leaving it unclear if the disease increases the risk of hypertension and coronary heart disease (74). Overall, the findings of these clinical trials indicate that Alzheimer's disease comorbidities, particularly diabetes, are associated with poor COVID-19 outcomes.

COVID-19 has been linked to an increased risk of Alzheimer's disease development and progression

COVID-19 has been linked to mental illness.

Short-term cognitive impairment is seen in COVID-19 infected patients. All of the investigations found that individuals with global cognitive impairment had a greater rate than healthy controls. Regarding particular cognitive domains, it appears that attention and regulatory functions are susceptible. On the other hand, the evidence for memory, language, and visuospatial functions is less trustworthy.

Methodological heterogeneity, such as the type of instrument or test utilized, the period of evaluation (early vs. late in the disease process), inclusion and exclusion criteria, and the extent to which exact data was provided, may all contribute to the latter. Despite the lack of test data from similar SARS-CoV or Mers CoV infections (104), Rogers and colleagues (105)found that while one-third of patients showed cognitive impairments in the early stages, only one-fifth of patients had mental issues later on. De Lorenzo et al (106) found that one-fourth of COVID-19 patients had cognitive impairment after discharge, consistent with this conclusion. More research using similar approaches is needed to examine time gradients for mental damage following COVID-19.

COVID-19 survivors have a higher rate of cognitive impairment than controls, according to the findings of a significant internet-based study that included 84 285 COVID-19 survivors. COVID-19 infection causes mental damage across multiple cognitive domains, according to the survey. Unfortunately, only 361 of the participants tested positive for COVID-19, and the paper had not yet been peer-reviewed when we conducted our search, so it was excluded from our analysis. To present, only a few studies with 1,000 participants have been published on COVID-19's actual short-term cognitive effects. Patients who said they had mental problems ranged from 15% (107) to 80% (108).

SARS-potential CoV-2's entrance sites into the central nervous system

Cerebrospinal fluid

A network of blood capillaries known as choroid plexuses in the ventricle walls produces cerebrospinal fluid (CSF) in the brain (109). Eighty percent of CSF proteins come from blood, synthesized and released by CNS cells. As a result, any cellular or metabolic changes in the brain may impact the CSF. As a result, detecting SARS-CoV-2 in the CSF could provide information about the virus's potential to infect neurons. A COVID-19 patient with encephalitis had SARS-CoV-2 in his CSF. The right ventricle

wall was hyper intensified, and the hippocampus had aberrant findings (110). A patient with demyelinating disease experienced neurological symptoms, and a real-time polymerase chain reaction (RT-PCR) test revealed that the CSF sample was positive for SARS-CoV-2 (111). According to Cebrian and colleagues, SARS-CoV-2 was found in the CSF of a patient experiencing headaches and loss of consciousness (112). SARS-CoV-2 RNA was identified in the CSF of severe COVID-19 patients in a retrospective investigation evaluating neuroimaging results (113).

Antibodies to SARS-CoV-2 develop shortly after infection. As a result, following a viral infection, immune-mediated nervous system damage may develop. The finding of covid antibodies in the CSF of two patients with COVID-19 encephalopathy supported this notion. SARS-CoV-2 S and N protein antigens were identified using an enzyme-linked immunosorbent test (ELISA) (114). A brief intracellular C segment, a transmembrane moiety, and an ectodomain region make up the SARS-CoV-2 S proteins. The ectodomain's S1 component boosts receptor binding, but S2 increases cell adhesion and virus transmission to non-infected cells, promoting membrane fusion (115). By activating glial cells, these antibodies can generate proinflammatory cytokines. Neuroinflammation can result in cytokine production and oxidative stress. The detection of SARS-CoV-2 in CSF in COVID-19 infected patients with neurologic symptoms showed virus invasion into the CNS.

However, when analyzed retrospectively, SARS-CoV-2 was not discovered in 578 CSF samples from COVID-19 patients. The study was conducted in the general community, and the authors concluded that testing for SARS-CoV-2 in the CSF is unnecessary (116). SARS-CoV-2 was also not identified in the CSF of COVID-19-induced meningitis, encephalitis, or individuals with Guillain-Barré syndrome(117, 118). More investigation and documentation in large patients are needed if these neurologic symptoms are only present in a fraction of COVID-19 infected people. A rising number of research teams have tested SARS-CoV-2 in cerebral fluid, with varied findings. The test performance requirements, reliability, and reproducibility vary because CSF analysis is performed in different laboratories using different methodologies (129-131). Lumbar puncture's technical problems are a crucial constraint in collecting CSF biomarkers.

Furthermore, distinguishing between COVID-19-related neurological diseases is a diagnostic problem. COVID-19 patients' neurological symptoms can arise days after infection with SARS-CoV-2. CSF may have a low viral load because of the five-day incubation period and the time between infection and sample collection (138). As a result, more persons with neurological symptoms need to be tested with the CSF SARS-CoV-2 assay. Because there is a lack of knowledge concerning COVID-19's potential neurologic effects, CSF studies correlating confirmed cases and neuropathological findings have been conducted.

Olfactory route

Anosmia and hyposmia, or a loss or decreased capacity to smell, have been found as an early COVID-19 indication. Several research investigating the prevalence of olfactory impairment in COVID-19 patients, as well as the clinical results, have recently been published(119, 120). Given that the olfactory route may allow easy access to the CNS, it is impossible to rule out the likelihood of SARS-CoV-2 adopting this route. The concept of SARS-neuroinvasive CoV-2's potential has grown increasingly elusive as a growing number of clinical research aimed at discovering the association between the olfactory pathway and neurotropism in COVID-19 infected persons have surfaced.

Olfactory neurons (OSN) in the olfactory epithelium trigger the olfactory response. Cilia that project from olfactory nerve cells' dendrites can infect neurons with the virus(121). The cribriform plate of the ethmoid bone is where OSN axons travel. Axon bundles form the right and left olfactory nerves, which end in the brain's olfactory bulbs (122) (See Fig. 2 for further information) SARS-CoV-2 infection needs S protein affinity for the ACE2 receptor, followed by TMPRSS2 activity (24). ACE2 receptor and TMPRSS2 were found in considerable numbers in cilia-lined goblet cells and nasal mucosal cells in several RNA-seq datasets (123). Nasal initial installation of two strains of SARS-CoV-2 (UCN1 and UCN19) caused olfactory epithelial damage, loss of OSN cilia, and immune cell intrusion in the olfactory epithelium in the golden Syrian hamster model (124).

In thirty-two COVID19 patients after autopsy, the greatest amount of SARSCoV2 was detected in the olfactory mucosa under the cribriform plaque, olfactory bulb, trigeminal ganglia, and elongated medulla (125). Despite this, MRI scans revealed bilateral olfactory edema in an asymptomatic healthcare worker who subsequently developed anemia and dysfunction after being diagnosed with SARSCoV2 and subsequently development of arrhythmias and developmental disorders (126).

In a superstructural study of the olfactory nerve, rectal gyrus, and brain of COVID19 patients, damage to axons, stroma, and myelin sheath

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was observed. SARSCoV2 virions have also been found in different anatomical locations (127). This notion is supported by brain MRI studies in COVID-19 patients, which show that the olfactory bulb was affected due to the SARS-CoV-2 infection (128, 129).

Trigeminal nerve

The COVID19 neuronal abnormalities may be due to SARSCoV2 entry into the trigeminal sensory axon from the nasal mucosa. Autopsy of the trigeminal nerve of six COVID19 patients revealed neuronal loss and axonal degeneration. However, it is not known whether these findings are due to an immune response or a direct viral entry. Sensory axons of the ophthalmic, maxillary, and mandibular nerves of the trigeminal nerve enter the trigeminal ganglion and terminate with bridging nuclei. In the trio of corpses of individuals infected with COVID19, SARSCoV2 was found in large numbers. Another remarkable feature of the SARSCoV2 trigeminal nerve interaction is the connection of the trigeminal nerve to the caudal regions of the brain and to the respiratory nuclei. This lends credence to the idea that SARSCoV2 can damage the nuclear tract solitary cells (NTS) in COVID19 patients, leading to microvascular coagulation, pulmonary edema, and a cytokine storm.

Hematogenous route

it can infect the endothelial cells of the blood-brain barrier or the lining of the plasma-liquid barrier (BCSF) in the ventricles through this transfection pathway (130). Paracellular transmigration, which occurs when the BBB's tight connections are disturbed, can allow viruses to reach the CNS (131). SARS-CoV-2 can enter the bloodstream and go to the CNS, where it attaches to ACE2 receptors (152ACE2 receptors are located on neuronal cells and glia and aid SARS-CoV-2 infiltration) (132). This may explain why glial-fibre acid protein (GFAP), a biomarker of astrocyte injury, and nerve fiber light chains, a diagnostic of neuronal damage, are both elevated. go up (133, 134). When comparing COVID-19 patients with CNS symptoms to COVID-19 patients without CNS symptoms, the patients with CNS symptoms had a lower lymphocyte count. This could be linked to the SARS-CoV-2-mediated decrease of immunity (3). Other explanations include the occurrence of a cytokine storm and the avoidance of T-cell regulation by SARSCoV2 infection (135).

Dissemination of neurons

Respiratory viruses can infect peripheral neurons before infecting axonal transport networks, allowing retrograde neural propagation into the CNS. Viruses that infect sensory or motor nerve terminals can use the peripheral organs as an entrance point since they are related to the CNS neurons (136). Both were receiving and transmitting information is possible with polarised neurons. Dynein and kinesin are proteins that help with anterograde and retrograde transport, respectively (137). The existing data, which are summarised in this study and explain the role of SARS-CoV-2 in a variety of neurological disorders, support a convergent notion that axonal dispersion plays a significant role in disease progression.

Gastrointestinal tract

COVID19 patients are also concerned about the likelihood of SARSCoV2 transmission through the intestine. The prevalence of ACE2 receptors in the stomach, duodenal, and rectal epithelium might explain this (138). ACE2 receptors have been discovered in colon endothelial cells, in addition to artery smooth muscle and arterial smooth muscle. An immunohistochemistry research revealed the presence of ACE2 receptors in the small intestine (139). COVID19 individuals have revealed a link between disease and digestive system disturbance, indicated by diarrhoea, nausea, vomiting, and abdominal discomfort, due to the broad distribution of ACE2 receptors (140). This might explain why SARSCoV2 was found in the patient's faeces five weeks after the upper respiratory tract swab was negative (141). The vagus and sympathetic nerves govern the enteric neural network, which links the gastrointestinal tract to the central nervous system. SARSenteric CoV2 infection can impact the lymphatic and blood systems. COVID19 individuals with SARSCoV2 RNA in their faeces had a 67 percent suppression rate.

COVID-19: post syndrome

Patients who have experienced a severe COVID19 episode may develop post COVID syndrome, which affects around 10% of COVID19 patients. Post-COVID syndrome symptoms are frequently mild, improve with time, and have no proven predictors. Fatigue, dyspnea, chest discomfort, mental health concerns, and long-term olfactory and gustatory anomalies are the most common symptoms of post COVID syndrome. Patients suffering from post-COVID syndrome will almost certainly be treated mostly through general care. This study discusses the impact of these complicated difficulties on patients with post-COVID syndrome, as well as the need for quick diagnosis based on well-defined criteria. Patients with post-COVID syndrome should be treated symptomatically, taking any pre-existing or new diseases into account. Recommendations for the assessment and management of post-COVID illness based on recognised criteria are necessary in order to

provide appropriate medical care. Furthermore, an active and comprehensive follow-up of COVID19 patients is necessary to investigate the incidence, clinical spectrum, and prognosis of individuals who have developed post-COVID syndrome (142).

Prospects

The SARS-CoV-2 infection has been shown to significantly reduce Alzheimer's disease symptoms linked to the inflammatory system in the brain, as well as the fact that particular viral access components are highly articulated in blood-brain barrier cells. These findings imply that the virus may possibly affect several genes or biochemical pathways in neuroinflammation and microvascular damage in the brain, potentially leading to cognitive decline similar to Alzheimer's disease. For the study, the researchers used data from COVID-19 and Alzheimer's patients. They used artificial intelligence to determine the distance between SARS-CoV-2 gene products and those linked to other neurological disorders, with closer closeness indicating related or comparable disorder pathways. The scientists looked at the genetic factors that allow the SARS-CoV-2 virus to infect brain cells and tissue. The researchers discovered a strong relationship between SARS-CoV-2 and genes/proteins linked to mental illnesses like Alzheimer's. As a result, COVID-19 might be a cause of Alzheimer's-like dementia. Furthermore, those with the APOE E4/E4 variant showed lower antiviral defence gene expression, which might explain why certain people are more sensitive to viruses.

Conclusions

Through the use of SARS-CoV-2, a global COVID-19 outbreak has been created. SARS-CoV-2 can enter the central nervous system via extramedullary and cognitive routes, causing neurological problems such as cognitive loss, systemic inflammation, APP metabolic dysfunction, long-term hospitalisation, and coma, among other things. Alzheimer's disease (AD) is one of the most prevalent CNS outcomes, resulting in disproportionate costs for patients, the community, and enterprises, according to COVID-19. COVID-19 mortality and morbidity are much higher in Alzheimer's patients due to age, Alzheimer's-related psychiatric issues, drug-drug combinations, dietary challenges, and a loss of self-care and cognitive skills. Furthermore, within the COVID-19 epidemic, unaffected Alzheimer's patients are both impacted and protected by isolation or a touch limit. As a result, our findings highlight the need for more research in this area. Identifying the mechanisms by which SARS-CoV-2 infects CNS cells; thoroughly investigating the causes of increased COVID-19 mortality in Alzheimer's disease patients and developing treatment strategies; demonstrating the effects of COVID-19 on AD-relevant pathophysiology and behavioural changes using animal research and patient samples; and constructing a picture of the relationship between COVID-19 and Alzheimer's disease.

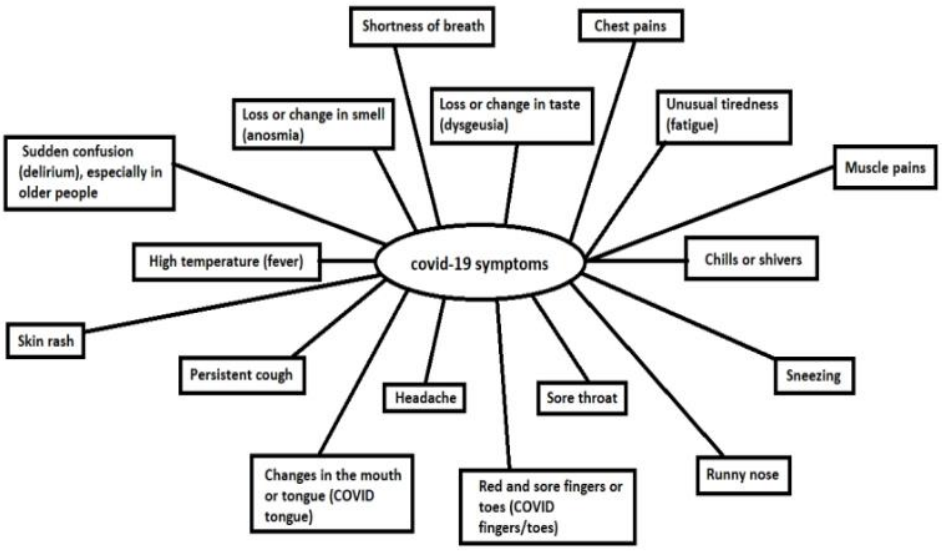

Figure 1.most common symptoms of covid-19

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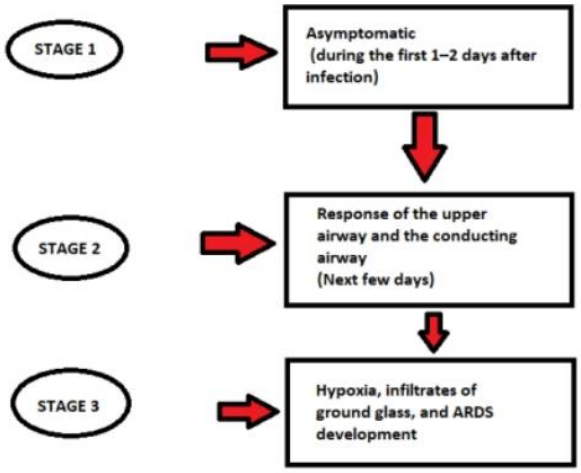

fig, stages of covid pathogenesis

Figure 2. stages of covid pathogenesis

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