REVIEW

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Impact of COVID-19 infection in patients with neurodegenerative diseases with particular focus on Alzheimer's and Parkinson's disease

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Neurodegenerative disorders (NDD) are chronic neurological diseases characterized by loss and/or damage to neurons along with the myelin sheath, and patients are at higher risk of severe infection with the SARS-CoV-2. A comprehensive literature search was performed using relevant terms and inclusion-exclusion criteria. Recent articles, subjects older than 50 years, and articles written in the English language were included, whereas letters to the editor and articles related to pregnant women were excluded from the review study. COVID-19 appears to damage angiotensin-II receptors which cause natural killer cells to lose the ability to clear virus-infected cells, owing to worse outcomes in patients with NDD. COVID-19 can worsen the symptoms of Alzheimer's disease. In addition, COVID-19 worsens drug-responsive motor symptoms in Parkinson's disease (PD) and other symptoms like fatigue and urinary complaints. Vitamin D is essential in decreasing pro-inflammatory and increasing anti-inflammatory cytokines in ongoing COVID-19 infections and reducing angiotensin receptors and, hence, decreasing COVID-19 infection severity. Telemedicine shows promise for patients with NDD but is yet to overcome legal issues and personal barriers. COVID-19 has a significant effect on neurodegenerative conditions, which appears partly to the nature of the NDD and the neuro-invasive capabilities of the SARS-CoV-2. The protective role of vitamin D in patients with NDD further supports this hypothesis. Modifications in current health care, like the telemedicine platform, are required to address the increased risk of serious infection in this population. Further studies will be required to clarify conflicting reports in many fields.

Key words: COVID-19, neurodegenerative diseases, telemedicine, anosmia

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INTRODUCTION

Coronaviruses are enveloped, single-stranded RNA viruses divided into five genera: α, β, γ, δ, and ε. The severe acute respiratory syndrome coronavirus (SARS-CoV-2) comes under beta-coronaviruses and is one of the seven coronaviruses known to affect humans (Williams, 2020). The SARS-CoV-2 quickly spread throughout the world from its origins in China due to its higher reproductive number, making it more transmissible (Zou et al., 2020). Extrapulmonary manifestations of the virus are now well established, with gastrointestinal, renal, and neurological presentations being the other systems afflicted by it (Moro et al., 2020). Neurological features like stroke, neuritis, and encephalopathy have been observed in recent months (Whittaker et al., 2020). It has been seen that the virus possesses the ability to invade the central nervous system in individuals with no history of neurological disease in the past and can lead to new neurological problems in people with COVID-19 (Mao et al., 2020). On top of that, the elderly and people with weakened immune systems are seen to have higher mortality because of the virus (Alzheimer's Disease Research Enterprise in the Era of COVID-19/SARS-CoV-2, 2020). Therefore, it is likely that the implications of this pandemic for individuals with neurodegenerative disorders will be of great concern.

The SARS-CoV-2 has definitely caused a pandemic, but there has been an ever-growing epidemic of neurodegenerative disorders, which has slowly but surely increased in the aging population (Katzman, 1976). Due to better awareness and screening, the number of neurodegenerative cases is about 60-70 million globally and is projected to double in the next twenty years (Nichols et al., 2019). In the United States, deaths due to Alzheimer's alone have increased by 33% in people aging 65 to 74 years, by 55% in people 75 to 84 years, and 78% in people 85 years and older (2020 Alzheimer's disease facts and figures, 2020). It is seen that diseases that involve systemic inflammation, like infections, sepsis, and trauma, pose a risk to the deterioration of neurodegenerative disorders (Giridharan et al., 2019; Walker et al., 2019). The cytokine storm, along with the systemic inflammation caused by SARS-CoV-2, put these individuals in a similar boat. A lot has been learned with time about the COVID-19 disease process, especially its neurological manifestations, including central and peripheral nervous system features like vomiting, headaches, dizziness, loss of taste, and loss of smell (Mao et al., 2020).

According to McAlpine et al. (2021), patients with multiple sclerosis (MS) had good outcomes, and disease-modifying therapies do not raise the risk for severe disease. Patients with dementia, including Alzheimer's disease, are at higher risk for hospitalization and death when compared to patients with preexisting Parkinson's disease (PD). Viral infections and their neuroinflammation have been associated with the pathogenesis of Alzheimer's disease, PD, and MS, suggesting that COVID-19 may have the potential to initiate or accelerate the neurodegeneration process. Since patients with Alzheimer's disease are at higher risk for death and hospitalization due to COVID-19, additional protective measures and precautions need to be implemented to prevent infections and also to optimize the management of comorbidities in this vulnerable population (McAlpine et al., 2021). Certain measures to periodically evaluate the COVID-19 patients with comprehensive cognitive and neuropsychiatric assessments and specific mental health and cognitive rehabilitation programs are required for individuals suffering from long-term cognitive symptoms (Alonso-Lana et al., 2020). More robustly designed studies are needed to determine whether COVID-19 may lead to an increased risk of developing NDD in susceptible individuals and to test the potential mitigating strategies to clarify and assess the long-term implications (McAlpine et al., 2021).

METHODS

A comprehensive literature search was done using PubMed, PubMed Central, ScienceDirect, Scopus, and Google Scholar. The study was searched using keywords like "COVID-19", "neurodegenerative," "telemedicine," and "anosmia." The literature search was performed by connecting keywords with the "OR" or "AND" boolean operator. We included all the articles from December 2019 to February 2022. We included the studies where the patients' age was greater than 50 years. Original articles were only included in the study, while animal or primitive studies and letters to the editor were excluded from the study.

DISCUSSION

Mechanism of entry of COVID-19 virus and its effects on the CNS

The mechanism of neurodegeneration involves the angiotensin-converting enzyme (ACE)-2 receptors and the iron proteins. SARS-COV-2 binds to the ACE-2 receptors and causes hydrolysis of the angiotensin II receptors, leading to the accumulation of receptors. Angiotensin II causes iron dyshomeostasis as this peptide

regulates several iron proteins, including hepcidin, divalent metal transporter-1 (DMT-1), ferroportin-1 (Fpn-1), and transferrin receptor-1 (TfR-1) (Chen et al., 2020). Angiotensin receptor blocker (ARB) is known to be protective against COVID 19 and neurodegeneration (Song and Kim, 2019). A potential relationship between hyperferritinemia and premature cellular senescence predisposes to both severe COVID-19 illness and diseases of the nervous system (Kale et al., 2020). According to Pereira et al. (2019), the impaired clearance of the senescent cells dysregulates both the lymphocytes and adjacent natural killer cells, further aggravating the degeneration. (Sfera et al., 2021).

After the passage of SARS-CoV-2 into the olfactory bulb, it conceivably brings about viral replication framing Th1, ORF3a, ORF8b, E, and other viral proteins. These proteins may likewise activate the (atomic factor kappa-light-chain-enhancer of initiated B cells) NF-kB pathway followed by other pro-inflammatory cytokines like TNF-α, interleukin-1b (IL-1b), and interleukin-6 (IL-6). It will uncover the noticeable proteins, for example, α-synuclein and amyloid filaments which could get aggregated in neurodegenerative diseases. This inflammation in the cerebrum could further trigger oxidative stress mediators like reactive oxygen species and nitrogen species. The loss of dopamine neurons or the accumulation of amyloid fibrils structures that collect to form insoluble strands resistant to degradation is the significant pathogenesis of Parkinson's and Alzheimer's disease (Mahalaxmi et al., 2021). In Alzheimer's disease, reactive astrocytes take up and degrade the pathogenic amyloid-β (Aβ) from the extracellular space. Also, the viral components such as the spike protein could stimulate toll-like receptor (TLR)-2 and TLR4, whereas viral RNA could stimulate TLR7 and TLR8. Synchronous stimulation of multiple TLRs could result in a severe increase in cytokine transcription leading to a cytokine storm in the CNS (Li et al., 2021).

In summary, COVID-19 invasion of ACE-4, DPP4, and furin increase the intracellular iron. The disaggregation of DNA strands and P53 damage together causes natural killer cells ferro senescence. The natural killer cells cannot remove the senescent, virus-infected cells and α-synuclein, developing SARS-CoV-2 severe illness and neurodegenerative disorders. Due to the high prevalence of olfactory dysfunction with age, it is critical to correlate the mechanism related to anosmia related to COVID-19. As measured by psychological, social, and electrophysiological tests, it is about 90% in Parkinson's and 85% in Alzheimer's disease (Doty, 2012; Woodward et al., 2017). Most of them are above 80 years of age, and about 62-80% suffer from these symptoms. The inflammatory mediators like cytokines, lymphocytes, and macrophages with immune cell interaction are supposed to be involved in this process of severe toxicity to the olfactory neurons (Rebholz et al., 2020).

Alzheimer's disease

Infection with SARS-CoV-2 lead to development of coronavirus disease 2019 (COVID-19) in humans. According to Alonso-Lana et al. (2020), in a patient with preexisting dementia, including AD, COVID-19 disease may present with unusual symptoms such as acute mental status changes including agitation, confusion, loss of orientation, or diarrhea in the absence of upper or lower respiratory tract symptoms such as cough or fever. This presentation could be misdiagnosed as from underlying worsening of neurodegenerative conditions (Alonso-Lana et al., 2020). Therefore, any AD patient presenting with clinical worsening of underlying disease should be suspected of COVID-19 in an appropriate clinical context.

Patients with a known diagnosis of neurodegenerative disorders such as AD are at increased risk of infection with SARS-CoV-2. According to Amruta et al. (2021) the diagnosis of AD is an independent predictor of severe COVID-19 disease, including hospitalization, and bears the increased risk for mortality even after the exclusion of co-existing risk factors. The increased risk for severe COVID-19 diseases in AD may be related to an increased predisposition to systemic and neuroinflammatory states (Rodriguez et al., 2020; McAlpine et al., 2021). It has been reported that the outcome of Alzheimer's patients infected with COVID-19 is reportedly much worse in those with underlying APOE homozygous e4 allele status compared to E3 status, independent of preexisting comorbidities. (Haghighi et al., 2020; Kuo et al., 2020) A significant proportion of dementia patients have reported worsening of cognitive abilities during the pandemic, including the decline in memory levels and reduced ability to perform activities of daily living (ADL) (Amruta et al., 2021). According to Alonso-Lana et al. (2020) in dementia patients hospitalized with COVID-19, hypoxic status or febrile conditions are common. Both of these have been known to precipitate a state of acute agitation. Additionally, acute agitation could lead to poor compliance with mechanical ventilation (Carrarini et al., 2021). This could lead to a vicious cycle since worsening of cognitive status by use of extensive mechanical ventilation has been reported in dementia patients in the literature (Alonso-Lana et al., 2020). The neurological worsening due to COVID 19 may not remain restricted to the acute course of the disease. There are reports of cognitive impairment at and after the discharge of patients (Helms et al., 2020).

Management of COVID-19 in patients with underlying Alzheimer's or Parkinson's disease requires careful consideration of drug interactions. These patients are on multiple drugs, such as cholinesterase inhibitors which have the potential for significant interactions with chloroquine, hydroxychloroquine, and lopinavir/ritonavir with concern for cardiac adverse events (Alonso-Lana et al., 2020).

Although the long-term consequences of SARS-CoV-2 and its effects on the brain are not fully understood, the field of AD research may benefit from understanding its possible role in future neurodegeneration. The "cytokine storm" of intense inflammation that results in an increase of pro-inflammatory cytokines such IL-1, and IL-6 is frequently linked to severe outcomes following SARS-CoV-2 infection (Naughton et al., 2020). This may combine with an amyloid-stimulated type I interferon (IFN) response in AD patients, resulting in the "perfect storm" (Naughton et al., 2020). This may help to explain why SARS-CoV-2 infection-related systemic inflammation may cause pre-symptomatic persons with undiagnosed AD to experience an acceleration of symptoms (Naughton et al., 2020). Other authors also proposed that after recovering from the first COVID-19 infection, affected patients may be more susceptible to cognitive loss (Bauer et al., 2014). Pathogenetically, this could be caused by the immune response's direct side effects, the escalation or amplification of pre-existing cognitive abnormalities, or the de novo initiation of a neurodegenerative illness. These results raise the possibility that there may be a population at risk for neurodegenerative disorders that are concealed by silent viral infections in the brain.

Parkinson's disease

The prevalence rate of SARS-CoV-2 infection in PD patients has been estimated to be approximately less than 1% (Yu et al., 2021). There is some literature suggesting an increased risk of SARS-CoV-2 infection in patients with a history of Parkinson's disease (Yu et al., 2021). However, based on close reading of most of the available scientific literature, it can be reasonably concluded that PD patients are not at higher risk for contracting SARS-CoV-2 infection compared to the non-PD population (Artusi et al., 2021; Fearon and Fasano, 2021; Ferini-Strambi and Salsone, 2021). No significant association has been noted for SARS-CoV-2 infection for the age of the patient and duration of PD between PD and non-PD control groups (Cilia et al., 2020b). COVID-19 does cause worsening of drug-responsive motor symptoms in infected PD patients when compared to the non-infected PD control population. This may be due to direct effects of the infection but could also be partly explained by indirect mechanisms such as alteration in pharmacokinetics of PD drugs due to COVID-19 induced diarrhea, drug interactions between drugs for PD and drugs for COVID-19. Specific non-motor symptoms of PD that appear to be worsened by COVID-19 include fatigue and urinary symptoms (urinary urgency and nocturia). The autonomic spectrum of PD patients does not appear significantly modified in infected PD patients (Cilia et al., 2020b; Fearon and Fasano, 2021; Ferini-Strambi and Salsone, 2021).

According to Artusi et al. (2021) the majority of COVID-19 infected PD patients may present with typical symptoms of viral prodrome. However, a significant proportion of patients may have atypical presentations, including worsening of parkinsonian symptoms like increasing motor symptoms or non-motor symptoms, fatigue, hypo-/anosmia, or painful limbs. Therefore, any PD patient presenting with clinical worsening of underlying disease should be suspected of COVID-19 in an appropriate clinical context (Fearon and Fasano, 2021). Although chronic neurological conditions such as PD have been reportedly associated with worse outcomes, including death from COVID-19 (Artusi et al., 2021), the overall literature appears inconclusive about the diagnosis of PD being an independent predictor of COVID-19 related death, usually confounded by factors such an age, the structure of study and comorbidities (Fearon and Fasano, 2021; Yu et al., 2021). As a corollary, at least 3 cases have been reported in the English language literature where the acute onset of parkinsonian symptoms was reported following SARS-CoV-2 infection, with no prior documented history of PD or genetic risk for PD or other parkinsonian conditions. The patients were all less than 60 years of age, with the youngest patient aged 35 years (Merello et al., 2021).

The clinical course of PD is complicated by COVID-19, which worsens both motor and non-motor symptoms, increases anxiety, and has serious negative effects on one's quality of life and mental health. Telemedicine has played a unique role during the COVID-19 era. To further understand the causative relationships between clinical and the severity of COVID-19, systemic inflammatory response with cytokine levels, and virus detection in the cerebrospinal fluid of PD patients, several cross-sectional and longitudinal investigations are, nevertheless, required.

Vitamin D role in COVID-19 and neurodegenerative disorders

Vitamin D has a crucial role in the innate immune system of individuals in various ways. Along with

toll-like receptors (TLRs), activated vitamin D increases the expression of cathelicidin and human beta-defensin-2 peptides. Cathelicidin interferes with bacterial cell membranes, even in viruses, especially enveloped viruses, impacting the viral entry. Vitamin D also helps deliver inflammatory mediators to the infection site. Vitamin D also leads to a reduction in pro-inflammatory cytokines linked with the Th1 response and a rise in anti-inflammatory cytokines linked with the Th2 immune response. According to Hribar et al. (2020), by down-regulating proinflammatory cytokines and up-regulating anti-inflammatory cytokines, vitamin D may be capable of preventing these severe complications related to COVID-19 and other viral illnesses. Meshkat et al. (2020) shows that vitamin D affects the pathogenesis of COVID-19 disease, and susceptible patients will benefit from supplementation in severe forms of this disease.

Neurodegenerative disorders, such as PD, is one of those that may be impacted by vitamin D levels. According to Hribar et al. (2020), PD patients with reduced dopamine synthesis present with tremors, bradykinesia, postural instability, and rigidity, along with depression, sleep disruptions, and bowel or bladder dysfunction. Idiopathic PD is associated with the interruption of the cellular signals and circuits due to vitamin D deficiency. The treatment regimens for PD are focused mainly on increasing these dopamine levels; however, these patients also showed benefit from exercise and complementary and alternative medicine methods such as vitamin D (Hribar et al., 2020). PD is typically a disease of the older populations, with more risk as age advances. One of the alternative therapies is the vitamin D consideration in elderly PD patients, as they are more susceptible to COVID-19. Several studies showed that vitamin D supplementation not only protects the patients from COVID-19 but also helps slow PD progression and improves the quality of life. As mentioned in Hribar et al. (2020), especially in PD patients without significant dementia, more substantial performances on neuropsychiatric tests were correlated with higher 25(OH)D3 levels in the blood. Vitamin D usage will enhance bone health, increase cognition and memory, reduce the risk of severe injury from falls, and better mood may lead to increased quality of life along with slowing disease progression in PD patients.

Vitamin D is also involved in the pathogenesis of AD, including antioxidant action, phagocytosis of amyloid-beta plaques, anti-inflammatory action, regulation of intraneuronal calcium, ischemic zone size reduction, neurotrophic agents, and regulation of choline acetyltransferase enzyme. According to Aghamollaii et al. (2020), vitamin D deficiency (< 30 ng/ml) is seen in 75% of AD patients, and among them, 23% were severely deficient (<10 ng/ml). This study confirmed with results that vitamin D supplementation is considered beneficial in people with Alzheimer's disease risk.

Studies show that low vitamin D levels potentially increase the risk and adverse effects of neurological/degenerative, motor, and cognitive issues. Vitamin D seems to impact both the motor and non-motor symptoms of PD. Vitamin D also seems to be linked with the pathogenesis of AD. Low levels of vitamin D among elderly individuals are more common due to decreased mobility, lesser time spent in sunlight, increase in adiposity, and reduced appetite leading to reduced rates of synthesis of vitamin D in the skin and reduced vitamin D absorption in the gut. Several studies also show that vitamin D may directly down-regulate the ACE2 receptor, decreasing the risk of COVID-19 infection. All this information so far shows that vitamin D deficiency has effects on neurodegenerative conditions such as PD, AD, and also in COVID-19 patients. Further research is required on the correlation between vitamin D and the ACE2 receptor and how this may affect COVID-19 risk and pathogenesis. Also, studies are still needed on the data regarding daily supplementation with 2000–5000 IU/day of vitamin D3 in PD patients and its benefits in reducing the risk and severity of COVID-19.

Anosmia in COVID-19 when compared to age-related neurodegenerative disease

COVID-19 is very common in humans and has the potential to enter the brain without causing obvious clinical signs. The central nervous system (CNS), a tangle of cellular and molecular connections, keeps life going and keeps homeostasis in check. Unfortunately, if a viral infection is present in the CNS, whether acute, persistent, or latent, the immune system fails to respond, resulting in neurological disorders. The significant SARS-CoV-2 infection has caused havoc because of its potential for neuronal penetration and may have long-term consequences for those who are infected. According to a study by et al., SARS-CoV-2 may have the potential to infect neural cells and spread from the CNS to the periphery *via* trans neuronal routes (Das et al., 2020). It's also possible that the infection is neuro-invasive, with the ability to reach the brain *via* the olfactory bulb (Gómez-Iglesias et al., 2020; Xydakis et al., 2020). Many neurodegenerative illnesses, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, have a notable clinical feature of anosmia caused by olfactory dysfunction pathology (Hawkes, 2003; Rebholz et al., 2020). The degree of olfactory dysfunction in many neurodegenerative diseases varies and occurs along with other symptoms in the late stage of the disease (Doty, 2017; Rebholz et

al., 2020). Unlike other neurological diseases, anosmia resulting from the destruction of olfactory mucosa has been ascertained as the non-motor early clinical feature of PD (Doty, 2017). The SARS-CoV-2 infection has been predicted as a potential risk factor for developing Parkinsonism-related symptoms in a significant portion of COVID-19 patients and survivors (Brundin et al., 2020; Sulzer et al., 2020). The SARS-CoV-2 infection appears to induce defects in the dopamine system and loss of DA neurons which is known as the underlying cause of Parkinson's disease (Li et al., 2020a, 2020b; Yavarpour-Bali and Ghasemi-Kasman, 2020; Merello et al., 2021). Moreover, Parkinson's disease patients have been reported to be highly susceptible to SARS-CoV-2 infection, and COVID-19 related pathogenic changes appear to exacerbate the disease (Brundin et al., 2020; Sulzer et al., 2020). SARS-CoV-2 has also been confirmed to infiltrate the CNS through the olfactory bulb, causing cytokine storm, brainstem dysfunction, and neuronal death (De Santis, 2020). This SARS-CoV-2 within the CNS pathway raises concerns about a potential common connection between COVID-19 and smell dysfunctions, which may play a role in the development of multiple neurodegenerative disorders. Reports have suggested that smell or olfactory dysfunction is a sensitive disorder for various neurodegenerative diseases such as PD, AD, and dementia (Ponsen et al., 2004; Velayudhan and Lovestone, 2009; Doty, 2013). The basal forebrain cholinergic system, which controls multiple neurotransmitters in the brain, is a major player in smell dysfunction. When a foreign agent invades the CNS, cholinergic neurons project into the olfactory bulb and modulate different neuronal activities that induce an immune response. When cholinergic neurons are damaged or defective, this may trigger the M1 phenotype and excite inflammatory mediators including IL-6, IL-12p40, IL-15, and TNF to high levels, resulting in neuroinflammation and cell death (Doursout et al., 2013). When M1 phenotypes are activated, they can release pro-inflammatory cytokines or increase phagocytosis or apoptosis, both of which may lead to the development of neurodegenerative diseases (Seo et al., 2018). After SARS- CoV-2 enters the olfactory bulb, viral replication occurs, resulting in the formation of OFR3a, ORF8b, E, and other viral proteins. These proteins may also activate the (nuclear factor kappa-light-chain-enhancer of activated B cells) NF-kB pathway followed by other pro-inflammatory cytokines such as TNF-α, IL-1b, and IL-6. This will bring to light the prominent proteins such as α-synuclein and amyloid fibers which could get accumulated in neurodegenerative disorders. This inflammatory environment in the brain could also cause the collection of oxidative stress mediators including reactive oxygen and nitrogen species, ultimately leading to the destruction of dopamine neurons, similar to the pathogenesis of Parkinson's disease, or the accumulation of amyloid fibrils. These fibrils are soluble proteins that assemble to form insoluble fibers resistant to degradation, which is the core pathogenesis of Alzheimer's disorders (Hassanzadeh and Rahimmi, 2018).

COVID-19 affects many organs of our body, and one of its main features is anosmia too. Many studies have shown the role of cytokine storm, and oxidative stress mediators, including reactive oxygen and nitrogen species, in inducing damage to the olfactory bulb in the CNS leading to anosmia. This anosmia is very difficult to differentiate from anosmia arising in neurodegenerative diseases like Parkinson's and Alzheimer's disease, which have key features of destruction of dopaminergic neurons and accumulation of amyloid fibrils, respectively. It is also known that anosmia occurring in COVID-19 indicates a milder form of the disease. But more studies need to be carried out to investigate the cause of anosmia in neurodegenerative disease in order to differentiate it from anosmia arising from COVID-19.

Challenges and opportunities of telemedicine in patients with neurodegenerative disorder

Neurodegenerative diseases (NDDs) are characterized by constant deterioration of cognitive or motor functions, which makes traveling to the medical centers stressful and difficult for the patients and the caregivers. Measures executed to reduce the spread of the COVID-19 virus have forced social distancing and cancelation of cognitive stimulation programs, which may have contributed to behavioral symptoms, has generated loneliness, and worsened cognition in people with dementia. According to Alonso-Lana et al. (2020), COVID-19 has affected the functioning of memory clinics, clinical trials, and research programs in the Alzheimer's field, leading to the implementation of telemedicine. According to De Marchi et al. (2021), studies have evaluated the efficacy of cognitive tests, which are commonly used during face-to-face visits when administered during telemedicine. Telemedicine may also affect patients' cognitive rehabilitation through virtual or augmented reality. According to De Marchi et al. (2021), during this COVID-19 pandemic, while the health services for chronic patients were abruptly interrupted, the necessity to shift to alternative types of care, such as telehealth and telemedicine, has become obligatory in preventing further decline in functional activity (Geddes et al., 2020). Recently, the impact of the COVID-19 pandemic has forced the scientific community to redefine and enhance telemedicine's role in

the healthcare system; for instance, recent recommendations and guidelines have highlighted the significance of telemedicine in replacing outpatients' visits (Cilia et al., 2020a; Papa et al., 2020). Specifically, in this pandemic, telemedicine and telehealth access may be useful tools for facing its challenges. Augmenting telehealth would also reduce person-to-person contact, therefore reducing the risk of exposure for patients. PD is mainly visually evaluated and, hence, well suited to Telemedicine; therefore, this can be an essential means for assessing and managing the patients. The International Parkinson and Movement Disorders Society have updated a guide to telemedicine to tackle the recent challenges (International Parkinson Disease and Movement Disorder Society). Various recommendations are being provided, particularly in the management of advanced therapies and rehabilitation (Fasano et al., 2020; Miocinovic et al., 2020; Quinn et al., 2020; Srivastav and Samuel, 2020; Zhang et al., 2021). People worldwide have reported on the effectiveness of various forms of telehealth for monitoring ALS patients during the COVID-19 pandemic. According to De Marchi et al. (2021), at the beginning of the pandemic, the members of the Northeast ALS (NEALS) Consortium were surveyed in the US. ALS academic medical centers to investigate the possibility of continuing to follow up on ALS patients, approximately 50% of patients were unable to attend appointments in-person, but many could attend video appointments (Andrews et al., 2020).

Since the recent COVID-19, as the visits to clinics were interrupted, telemedicine has been confirmed as a good tool to monitor patients' clinical progression of dementia through the administration of cognitive tests and self-administered questionnaires. Telemedicine is challenging since not all patients have their own or can use devices such as computers, smartphones, or tablets due to accessibility or independent usage issues in long-term care clinics. There are several telehealth challenges that arise due to a range of considerations;

(a) legal issues dealing with data integrity, security tracking, and reporting (Bassan, 2020)
(b) personal barriers such as patients' barriers are related to personal complexity in the use of technology, due to motor limitations, added to the absence of dedicated caregivers and adequate setting
(c) differences with an in-person evaluation due to varied techniques for optimizing telemedicine interactions and equipment as training programs for neurologists are required in telehealth (Grossman et al., 2020)
(d) further research and clinical trial designs are necessary for the field of telemedicine which could be integrated with physician measures.

Together with new encouraging models of care, concerns about telemedicine becoming a new gold standard of treatment have also been raised; therefore, additional research is warranted to elucidate the benefits and limitations of telemedicine in NDD patients (Mulroy et al., 2020).

Limitation

There are a few limitations to the study. We did not include patients younger than 50 years, although some diseases like Huntington's disease are common in young adults, on which there could be an impact of COVID-19. Furthermore, there needs to be more research carried out to differentiate anosmia resulting from COVID-19 from anosmia occurring due to neurodegenerative diseases.

CONCLUSION

COVID-19 has a significant impact on the natural history of neurodegenerative conditions such as Alzheimer's and Parkinson's disease. The underlying basis of this association is still being understood; however, it appears partly related to the nature of the underlying disease process and the neuroinvasive potential of the SARS-CoV-2. This pathophysiological link is further supported by the protective effect of vitamin D in AD and PD patients. The worsened outcomes of AD patients with COVID-19 show significant association. In fact, vitamin D tempers the course of neurodegenerative conditions in COVID-19 patients. Contrarily the significance of the association of prognosis of PD patients infected with COVID-19 is not fully clear. The risks associated with SARS-CoV-2 infection in this patient population warrant important modifications in current health care delivery, including extensive use of the telemedicine framework. Further research is required in this field to resolve the conflicting evidence on many subtopics, including but not limited to whether PD is an independent risk factor for COVID-19.

REFERENCES

2020 Alzheimer's disease facts and figures (2020) Alzheimer's Dement 16: 391–460.

Aghamollaii V, Tafakhori A, Meshkat S, Shafieyoun A, Salimi A (2020) Vitamin D level in Alzheimer's disease: A case control study. Tehran Univ Med J 78: 16–20.

Alonso-Lana S, Marquié M, Ruiz A, Boada M (2020) Cognitive and neuropsychiatric manifestations of COVID-19 and effects on elderly individuals with dementia. Front Aging Neurosci 12: 588872.

Alzheimer's Disease Research Enterprise in the Era of COVID-19/ SARS-CoV-2 (2020) Alzheimers Dement 16: 587–588.

Amruta N, Chastain WH, Paz M, Solch RJ, Murray-Brown IC, Befeler JB, Gressett TE, Longo MT, Engler-Chiurazzi EB, Bix G (2021) SARS-CoV-2 mediated neuroinflammation and the impact of COVID-19 in neurological disorders. Cytokine Growth Factor Rev 58: 1–15.

Andrews JA, Berry JD, Baloh RH, Carberry N, Cudkowicz ME, Dedi B, Glass J, Maragakis NJ, Miller TM, Paganoni S, Rothstein JD, Shefner JM, et al. (2020) Amyotrophic lateral sclerosis care and research in the United States during the COVID-19 pandemic: Challenges and opportunities. Muscle Nerve 62: 182–186.

Artusi CA, Romagnolo A, Ledda C, Zibetti M, Rizzone MG, Montanaro E, Bozzali M, Lopiano L (2021) COVID-19 and Parkinson's disease: what do we know so far? J Parkinsons Dis 11: 445–454.

Bassan S (2020) Data privacy considerations for telehealth consumers amid COVID-19. J Law Biosci 7: 1–12.

Bauer K, Schwarzkopf L, Graessel E, Holle R (2014) A claims data-based comparison of comorbidity in individuals with and without dementia. BMC Geriatr 14: 10.

Brundin P, Nath A, Beckham JD (2020) Is COVID-19 a perfect storm for Parkinson's disease? Trends Neurosci 43: 931–933.

Carrarini C, Russo M, Dono F, Barbone F, Rispoli MG, Ferri L, Pietro M Di, Digiovanni A, Ajdinaj P, Speranza R, Granzotto A, Frazzini V, et al. (2021) Agitation and dementia: prevention and treatment strategies in acute and chronic conditions. Front Neurol 12: 644317.

Chen YJ, Qian ZM, Sheng Y, Zheng J, Liu Y (2020) Angiotensin II down-regulates transferrin receptor 1 and ferroportin 1 expression in Neuro-2a cells via activation of type-1 receptor. Neurosci Lett 716.

Cilia R, Bonvegna S, Straccia G, Andreasi NG, Elia AE, Romito LM, Devigili G, Cereda E, Eleopra R (2020a) Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. Mov Disord 35: 1287–1292.

Cilia R, Mancini F, Bloem BR, Eleopra R (2020b) Telemedicine for parkinsonism: A two-step model based on the COVID-19 experience in Milan, Italy. Parkinsonism Relat Disord 75: 130.

Das G, Mukherjee N, Ghosh S (2020) Neurological insights of COVID-19 pandemic. ACS Chem Neurosci 11(9): 1206–1209.

De Marchi F, Contaldi E, Magistrelli L, Cantello R, Comi C, Mazzini L (2021) Telehealth in Neurodegenerative diseases: opportunities and challenges for patients and physicians. Brain Sci 11: 1–20.

De Santis G (2020) SARS-CoV-2: A new virus but a familiar inflammation brain pattern. Brain Behav Immun 87: 95.

Doty RL (2013) Smell and the degenerating brain. The Scientist 27: 33–37.

Doty RL (2012) Olfaction in Parkinson's disease and related disorders. Neurobiol Dis 46: 527–552.

Doty RL (2017) Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? Lancet Neurol 16: 478–488.

Doursout MF, Schurdell MS, Young LM, Osuagwu U, Hook DM, Poindexter BJ, Schiess MC, Bick DLM, Bick RJ (2013) Inflammatory cells and cytokines in the olfactory bulb of a rat model of neuroinflammation; insights into neurodegeneration? J Interf Cytokine Res 33: 376.

Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, Foltynie T, Volkmann J, Merello M (2020) Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: The COVID-19 experience. Mov Disord Clin Pract 7: 361–372.

Fearon C, Fasano A (2021) Parkinson's disease and the COVID-19 pandemic. J Parkinsons Dis 11: 431–444.

Ferini-Strambi L, Salsone M (2021) COVID-19 and neurological disorders: are neurodegenerative or neuroimmunological diseases more vulnerable? J Neurol 268: 409–419.

Geddes MR, O'Connell ME, Fisk JD, Gauthier S, Camicioli R, Ismail Z (2020) Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19. Alzheimer's Dement 12.

Giridharan V V., Masud F, Petronilho F, Dal-Pizzol F, Barichello T (2019) Infection-induced systemic inflammation is a potential driver of Alzheimer's disease progression. Front Aging Neurosci 11: 122.

Gómez-Iglesias P, Porta-Etessam J, Montalvo T, Valls-Carbó A, Gajate V, Matías-Guiu JA, Parejo-Carbonell B, González-García N, Ezpeleta D, Láinez JM, Matías-Guiu J (2020) An online observational study of patients with olfactory and gustory alterations secondary to SARS-CoV-2 infection. Front Public Heal 8: 243.

Grossman SN, Han SC, Balcer LJ, Kurzweil A, Weinberg H, Galetta SL, Busis NA (2020) Rapid implementation of virtual neurology in response to the COVID-19 pandemic. Neurology 94: 1077–1087.

Haghighi MM, Kakhki EG, Sato C, Ghani M, Rogaeva E (2020) The intersection between COVID-19, the gene family of ACE2 and Alzheimer's disease. Neurosci Insights 15: 2633105520975743.

Hassanzadeh K, Rahimmi A (2018) Oxidative stress and neuroinflammation in the story of Parkinson's disease: Could targeting these pathways write a good ending? J Cell Physiol 234: 23–32.

Hawkes C (2003) Olfaction in neurodegenerative disorder. Mov Disord 18: 364–372.

Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F (2020) Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 382: 2268–2270.

Hribar CA, Cobbold PH, Church FC (2020) Potential role of vitamin d in the elderly to resist COVID-19 and to slow progression of Parkinson's disease. Brain Sci 10: 284.

International Parkinson Disease and Movement Disorder Society https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice--A-Step-by-Step-Guide.htm. Accessed March 24, 2022.

Kale A, Sharma A, Stolzing A, Stolzing A, Desprez PY, Desprez PY, Campisi J, Campisi J (2020) Role of immune cells in the removal of deleterious senescent cells. Immun Ageing 17: 1–9.

Katzman R (1976) The prevalence and malignancy of Alzheimer disease: a major killer. Arch Neurol 33: 217–218.

Kuo CL, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, Melzer D, Newman AB (2020) ApoE e4e4 Genotype and Mortality With COVID-19 in UK Biobank. J Gerontol A Biol Sci Med Sci 75: 1801–1803.

Li J, Long X, Zhu C, Wang H, Wang T, Lin Z, Li J, Xiong N (2020a) Olfactory dysfunction in recovered coronavirus disease 2019 (COVID-19) patients. Mov Disord 35: 1100–1101.

Li L, Acioglu C, Heary RF, Elkabes S (2021) Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. Brain Behav Immun 91: 740–755.

Li WS, Chan LL, Chao YX, Tan EK (2020b) Parkinson's disease following COVID-19: causal link or chance occurrence? J Transl Med 18: 1–3.

Mahalaxmi I, Kaavya J, Mohana Devi S, Balachandar V (2021) COVID-19 and olfactory dysfunction: A possible associative approach towards neurodegenerative diseases. J Cell Physiol 236: 763–770.

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, et al. (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 77: 683–690.

McAlpine LS, Fesharaki-Zadeh A, Spudich S (2021) Coronavirus disease 2019 and neurodegenerative disease: what will the future bring? Curr Opin Psychiatry 34: 177.

Merello M, Bhatia KP, Obeso JA (2021) SARS-CoV-2 and the risk of Parkinson's disease: facts and fantasy. Lancet Neurol 20: 94–95.

Meshkat S, Salimi A, Joshaghanian A, Sedighi S, Sedighi S, Aghamollaii V (2020) Chronic neurological diseases and COVID-19: Associations and considerations. Transl Neurosci 11: 294.

Miocinovic S, Ostrem JL, Okun MS, Bullinger KL, Riva-Posse P, Gross RE, Buetefisch CM (2020) Recommendations for deep brain stimulation device management during a pandemic. J Parkinsons Dis 10: 903–910.

Moro E, Priori A, Beghi E, Helbok R, Campiglio L, Bassetti CL, Bianchi E, Maia LF, Ozturk S, Cavallieri F, Zedde M, Sellner J, et al. (2020) The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection. Eur J Neurol 27: 1727–1737.

Mulroy E, Menozzi E, Lees AJ, Lynch T, Lang AE, Bhatia KP (2020) Telemedicine in movement disorders: Leçons du COVID-19. Mov Disord 35: 1893–1896.

Naughton SX, Raval U, Pasinetti GM (2020) Potential novel role of COVID-19 in Alzheimer's disease and preventative mitigation strategies. J Alzheimers Dis 76: 21–25.

Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, Aichour MTE, Akinyemi RO, Alahdab F, Asgedom SW, Awasthi A, Barker-Collo SL, et al. (2019) Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18: 88–106.

Papa SM, Brundin P, Fung VSC, Kang UJ, Burn DJ, Colosimo C, Chiang HL, Alcalay RN, Trenkwalder C (2020) Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. Mov Disord 35.

Ponsen MM, Stoffers D, Booij J, Eck-Smit BLF Van, Wolters EC, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 56: 173–181.

Quinn L, MacPherson C, Long K, Shah H (2020) Promoting physical activity via telehealth in people with Parkinson disease: the path forward after the COVID-19 pandemic? Phys Ther 100: 1730–1736.

Rebholz H, Braun RJ, Ladage D, Knoll W, Kleber C, Hassel AW (2020) Frontiers in Neurology.

Rodriguez M, Soler Y, Perry M, Reynolds JL, El-Hage N (2020) Impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the nervous system: implications of COVID-19 in neurodegeneration. Front Neurol 11.

Seo Y, Kim HS, Kang KS (2018) Microglial involvement in the development of olfactory dysfunction. J Vet Sci 19: 319.

Sfera A, Osorio C, Maguire G, Rahman L, Afzaal J, Cummings M, Maldonado JC (2021) COVID-19, ferrosenescence and neurodegeneration, a mini-review. Prog Neuropsychopharmacol Biol Psychiatry 109.

Song P, Kim JH (2019) Benefits of angiotensin receptor blockade: preventing smooth muscle cell senescence and beyond. Korean Circ J 49: 627–628.

Srivastav AK, Samuel AJ (2020) E-rehabilitation: one solution for patients with Parkinson's disease in COVID-19 era. Parkinsonism Relat Disord 75: 128.

Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, Al-Dalahmah O, Zecca L, Sette A, Bubacco L, Meucci O, Moro E, et al. (2020) COVID-19 and possible links with Parkinson's disease and parkinsonism: from bench to bedside. NPJ Park Dis 6.

Velayudhan L, Lovestone S (2009) Smell identification test as a treatment response marker in patients with Alzheimer disease receiving donepezil. J Clin Psychopharmacol 29: 387–390.

Walker KA, Ficek BN, Westbrook R (2019) Understanding the role of systemic inflammation in Alzheimer's disease. ACS Chem Neurosci 10: 3340–3342.

Whittaker A, Anson M, Harky A (2020) Neurological manifestations of COVID-19: A systematic review and current update. Acta Neurol Scand 142: 14–22.

Williams S (2020) The Scientist. https://www.the-scientist.com/news-opinion/a-brief-history-of-human-coronaviruses-67600. Accessed March 24, 2022.

Woodward MR, Amrutkar CV, Shah HC, Benedict RHB, Rajakrishnan S, Doody RS, Yan L, Szigeti K (2017) Validation of olfactory deficit as a biomarker of Alzheimer disease. Neurol Clin Pract 7: 5–14.

Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, Geisthoff UW, Bauer C, Hautefort C, Herman P, Manley GT, Lyon DM, Hopkins C (2020) Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis 20: 1015–1016.

Yavarpour-Bali H, Ghasemi-Kasman M (2020) Update on neurological manifestations of COVID-19. Life Sci 257.

Yu Y, Travaglio M, Popovic R, Leal NS, Martins LM (2021) Alzheimer's and Parkinson's diseases predict different COVID-19 outcomes: A UK Biobank study. Geriatr 6: 1–15.

Zhang C, Zhu K, Lin Z, Huang P, Pan Y, Sun B, Li D (2021) Utility of deep brain stimulation telemedicine for patients with movement disorders during the COVID-19 outbreak in China. Neuromodulation Technol Neural Interface 24: 337–342.

Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, et al. (2020) SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 382: 1177–1179.