Molecular Neurobiology (2021) 58:4477–4486
https://doi.org/10.1007/s12035-021-02408-8

The Intersection of Parkinson's Disease, Viral Infections, and COVID-19

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Received: 10 December 2020 / Accepted: 27 April 2021 / Published online: 25 May 2021

Abstract

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of human COVID-19, not only causes flu-like symptoms and gut microbiome complications but a large number of infected individuals also experience a host of neurological symptoms including loss of smell and taste, seizures, difficulty concentrating, decreased alertness, and brain inflammation. Although SARS-CoV-2 infections are not more prevalent in Parkinson's disease patients, a higher mortality rate has been reported not only associated with older age and longer disease duration, but also through several mechanisms, such as interactions with the brain dopaminergic system and through systemic inflammatory responses. Indeed, a number of the neurological symptoms seen in COVID-19 patients, as well as the alterations in the gut microbiome, are also prevalent in patients with Parkinson's disease. Furthermore, biochemical pathways such as oxidative stress, inflammation, and protein aggregation have shared commonalities between Parkinson's disease and COVID-19 disease progression. In this review, we describe and compare the numerous similarities and intersections between neurodegeneration in Parkinson's disease and RNA viral infections, emphasizing the current SARS-CoV-2 global health crisis.

Keywords Parkinson's disease · Viral infections · COVID-19 · Inflammation · Gut microbiome · Olfactory bulb

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder that primarily affects dopaminergic neurons in the substantia nigra [1]. Although this disorder mainly pertains to motor complication, PD patients also experience many non-motor symptoms such as neuropsychiatric (depression, dementia, apathy, anxiety), autonomic (constipation, urinary incontinence, excessive sweating), sleep disorders, and sensory abnormalities (loss of smell, pain, and paresthesia) [1]. The exact causes of sporadic PD are largely unknown, but it is clear that both environmental and genetic factors play a role. Indeed, the Braak hypothesis suggests that sporadic PD originates from an external pathogen that enters the body through the nasal cavity, which then migrates via the vagus nerve to the gut, causing complications such as changes in the gut microbiome and the advancement of Lewy Body (LB) pathology in the gut and in the nose similar to that of a viral infection [2, 3].

The novel SARS-CoV-2 coronavirus (COVID-19) pandemic was a result of a virus outbreak originating in Wuhan, China which quickly spread throughout the world. While flu-like symptoms such as fever, cough, and difficulty breathing appeared to be the predominant early warning signs of a COVID-19 infection, a large number of patients admitted to hospitals experienced a host of neurological symptoms including dizziness, loss of smell and taste, seizures, difficulty concentrating, decreased alertness, and brain inflammation [4]. In addition, complications in the gut microbiomes have also been noted as a result of COVID-19 [4].

Strikingly, a number of the neurological symptoms seen in COVID-19 patients, as well as the alterations in the gut microbiome, are also prevalent in patients with PD. Moreover, several biochemical pathways, including oxidative stress, inflammation, and protein aggregation, show similarities between PD and COVID-19. In this review, we describe the many intersections between neurodegeneration in PD and viral infections, with an emphasis on the novel SARS-CoV-2.

PD, Alpha-Synuclein, and RNA Viruses

The pathological hallmark of PD is the presence of LBs, neuronal inclusions constituted of aggregate protein [5]. The formation of LBs is seeded by the aggregation of its major component, the protein alpha-synuclein (a-syn). A-syn is an

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intrinsically disordered protein mainly found in neurons at the presynaptic terminals, but a-syn is also found in other tissues such as kidney, heart, and muscle cells [6]. While the physiological function of a-syn is not fully understood, a-syn has been implicated as a pre-synaptic protein that mediates neurotransmitter release [7, 8]. Duplications, triplications, and mutations of the a-syn encoding gene *SNCA* are linked to familial PD suggesting that an increase in a-syn and/or the expression of mutational variants contributes to neurodegeneration (Fig. 1) [9]. Many extrinsic factors such as post-translational modifications, oxidative stress, and metal binding have also been shown to affect multimerization and aggregation of a-syn, and due to its central effect on LB pathology, factors which affect the behavior or prevalence of a-syn are generally thought to be associated with PD [10, 11].

RNA viruses are linked to PD by their effect on a-syn (Table 1). For example, a-syn expression is upregulated in response to neurons infected by RNA viruses (Fig. 1) [12, 13]. It has been shown that a-syn supports expression of antiviral interferon-stimulated genes [12]. In fact, a-syn restricts RNA viral replication, protecting the central nervous system (CNS) in infected mice [14]. Interestingly, a-syn expression also increases in enteric neurons of the gastrointestinal tract in response to infections with the single-stranded RNA norovirus followed by an inflammatory immune response [15, 16]. While the prevention of RNA virus progression is of immediate and primary concern to an individual's health, elevated a-syn levels and prolonged inflammation are both linked to LB pathology and increased risk for PD [13].

The protective function of a-syn against RNA viruses has obvious implications to the novel coronavirus SARS-CoV-2, especially in individuals with PD. Elevated a-syn expression may indeed serve as a protective mechanism against this RNA-virus; however, it is unlikely that aggregated a-syn contained within LBs will be affective in restricting RNA viral replication. In addition to viral replication, a-syn can also inhibit RNA virus transmission from the peripheral nervous system (PNS) to the CNS [17]. When peripherally injected with a non-neuroinvasive RNA virus, the brains of a-syn knockout mice showed a much higher viral load than the brains of heterozygous a-syn expressing mice [14, 17]. In addition, the same difference was not observed when inoculation was done intracerebrally or done on brain slice cultures [14, 17]. Since COVID-19 can manifest itself in both the CNS and PNS, its replication and its spread may be inhibited by elevated a-syn in individuals living with PD or possibly other synucleinopathies [18].

Viral Infections and Neurotransmitters

With regards to viral infections, it has been noted that there is a link between viruses, neurotransmitters, and neurotransmitter protein pathways. The acetylcholine (ACh) and dopaminergic pathways are obstructed during PD, as a result of degeneration of the substantia nigra and motor neurons [19]. However, in the case of viral infections,

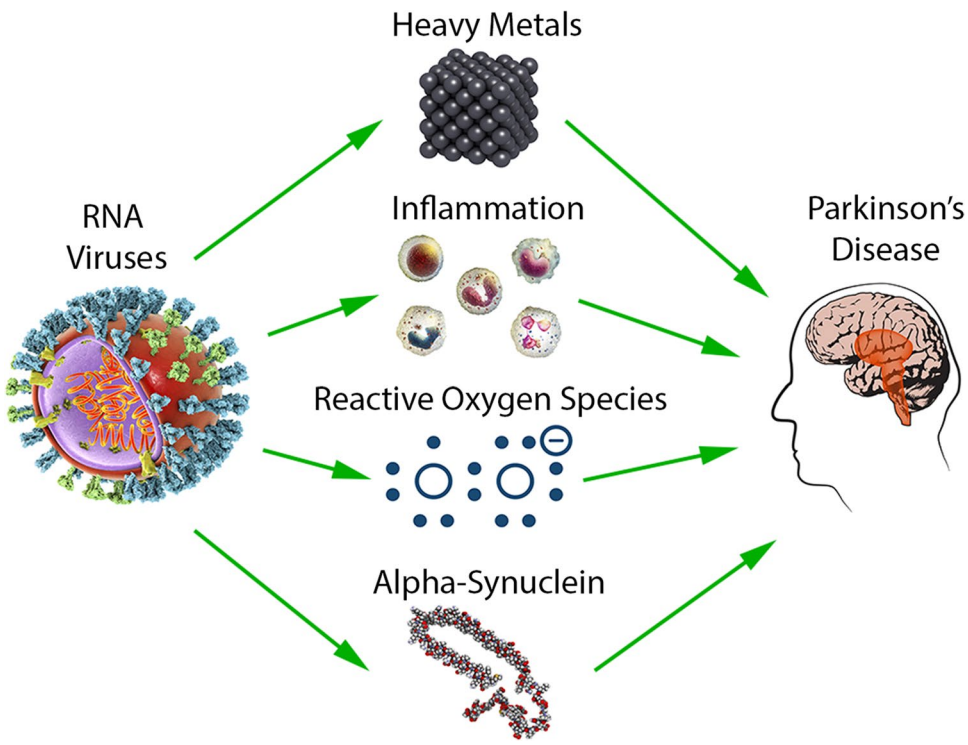

Fig. 1 Parkinson's disease contributing factors including heavy metals, inflammation, reactive oxygen species, and alpha-synuclein are elevated in response to RNA virus infection illustrating commonalities between neurodegeneration and viral infections

Table 1 Commonalities between Parkinson's disease and RNA virus infection

	Alpha-synuclein	Oxidative stress	Inflammation	Metals	Gut microbiome	Olfactory tract
Parkinson's disease	Aggregation leads to neurotoxic Lewy bodies [5]	Dysfunctional regulation of ROS by several genes including SOD1 leads to oxidative stress and apoptosis [16]	Protective short term, exacerbates non-motor symptoms long term [34, 36]	Exposure to heavy metals such as Mn is a risk factor for PD [42]	GI problems such as dysbiosis, constipation, and dysphasia [52]	Olfactory dysfunction is one of the earliest signs of PD [2, 3]
RNA virus infection	Upregulated in infected cells and restricts RNA virus replication [12–14]	Can create ROS imbalance causing DNA damage and neuroinflammation [23]	Neuro-inflammatory response can be triggered by infection [13, 35]	RNA virus replication depends on and may cause increase in Mn and Fe [42–44]	Microbiota depletion leads to GI issues causing inflammation and lack of gut flora [56]	Olfactory dysfunction is one of the earliest signs of COVID-19 infection [80, 81]

it has been shown that acetylcholine levels are affected throughout the progression of the virus. In the early stages of infection, acetylcholine levels seem to remain constant. However, ACh levels seem to rise around the peak point of the immune response. In addition, cholinergic lymphocytes, which make direct contact with macrophages in the lungs, appear as ACh levels increase which may be present as a result of the SARS-CoV-2 virus [20]. These lymphocytes, however, are also known to regulate pulmonary inflammation, a common symptom of COVID-19 [21]. In addition, it has also been shown that viruses lead to production of ACh via choline acetyltransferase (CHAT) enzyme activation [22]. With regards to recovery, however, the role of ACh is still unknown [21]. In addition to ACh, it has also been shown that viral infections play a role in the dopaminergic pathway. Theiler's virus, a type of encephalomyelitis RNA virus, has been known to destroy the substantia nigra, which is the site of dopamine production [23]. In an additional study involving mice, the presence of viral RNA was observed, and the viral RNA was present in the substantia nigra within 3 days of infection and spread further throughout the brain within 10 days. However, 3 weeks later, the viral RNA was no longer detected [23]. As a result, it could be argued that these interactions between the substantia nigra and viral pathogens may support the PD Braak hypothesis. Furthermore, the interactions between neurotransmitter pathways and viral infections may lead to further research regarding the intersection of viral infections such as COVID-19 and PD.

Oxidative Stress

Oxidative stress plays an important role PD and reactive oxygen species (ROS) and their extensive production in the brain play an important role in dopaminergic neuronal cell loss death involving dopamine metabolism and high levels of iron and calcium (Fig. 1) [24]. ROS are naturally occurring in cells and are a necessary component of cellular homeostasis. Despite the importance of ROS in normal physiology, failure in ROS regulation by antioxidant proteins, such as superoxide dismutase (SOD1) and glutathione (GSH), can lead to oxidative stress which can have detrimental effects on cellular functions (Table 1) [25]. Mitochondria are key sites of ROS production and targets of ROS-induced damage by inhibition of the mitochondrial election transport chain (ETC) [26]. PINK1 and Parkin are PD-associated proteins important in mitochondrial homeostasis as well as ROS homeostasis [26].

Many viruses, such as hepatitis C (HCV), are known to cause oxidative stress by changing the antioxidant balance

within cells (Fig. 1) [27]. HCV belongs to a family of RNA viruses that cause damage and cirrhosis of the liver and patients with chronic hepatitis C have increased ROS levels triggering immune responses and increased inflammation [28]. Another virus, Zika virus (ZIKV), which has been extensively studied due to its link with congenital malformations, has revealed that astrocytes are the targets of ZIKV [28]. In a recent study, it was shown that ROS imbalance, coupled with mitochondrial defects, trigger DNA damage in induced pluripotent stem cell (iPSC)–derived astrocytes, causing neuronal loss and motor defects [29]. Interestingly, ZIKV belongs to the *Flaviviridae* family of viruses, as does HCV, and it replicates within the endoplasmic reticulum (ER) causing an increase in ROS in both the ER and mitochondria [30, 31]. This increase in ROS causes breaks in DNA, activating the DNA damage response ultimately causing apoptosis [30, 31]. Reactive gliosis is a condition whereby neuroinflammatory conditions caused by bacterial or viral infections cause an inflammatory environment culminating in astrocyte reactivity [32]. These infected astrocytes correlate to an increase in pro-inflammatory chemokines and cytokines, and it has been speculated that surviving children infected by ZIKV might show an increased rate of neurological disorders such as PD or Alzheimer's disease (AD) later on in life [30, 31]. Although a definite connection is yet to be made between viral infections, such as ZIKV and hepatitis C, with respect to increased risk of sporadic PD it is noteworthy that increased ROS and mitochondrial dysfunction are found in both viral infections and in PD (Table 1).

Inflammation

Brain inflammation has long been implicated as a risk factor (Fig. 1) [33, 34], as well as a pathological effect of PD (Table 1) [35–38]. The primary facilitators of the neuroinflammatory response are microglia. Microglia release immune factors when activated in response to trauma, viral infection, and aggregated proteins such as a-syn [13, 39]. In addition, astrocytes can contribute to the inflammatory response when activated by RNA viral infection (Fig. 1) [40]. Neuroinflammation has been described as a double-edged sword in regards to PD as on one hand it is neuroprotective in the short term but acts in a neurotoxic manner when chronically sustained [39, 41]. Inflammatory cytokines, reported as increased in PD patients [42], have been shown to exacerbate cognition, depression, anxiety, and sleep disturbances [43, 44]. Similarly, COVID-19 patients have shown a wide range of neurological disorders including psychosis/delirium, inflammation of the brain, ischemic stroke, and multisystem inflammatory syndrome (Table 1) [45, 46]. Interestingly, pro-inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin (IL)-2, and IL-6 are found at higher levels in the brains of PD patients and the cerebrospinal fluid of COVID-19 patients [47, 48]. In addition, many COVID-19 cases result in a cytokine storm, a massive immune response that upregulates pro-inflammatory cytokines [49]. Increased inflammation, due to COVID-19 in PD patients, may exacerbate non-motor symptoms, and it has been suggested that PD patients recovering from COVID-19 show an extended period before reaching baseline. However, it is unclear if the exact mechanisms of inflammation in PD, MSA, and COVID-19 are the same.

Metals, Viral Infections, and PD

It has been noted that exposure to heavy metals such as manganese and iron has played a role in the progression of PD and other neurological diseases (Fig. 1) [50]. The most common form of exposure to these metals is a result of the environment and abnormal accumulations in the body. The presence of these metals results in multiple oxidative stress pathways that can lead to the oxidation of dopamine and production of free radicals [50]. Similarly, it has been noted that heavy metals also play a role regarding some viral infections. Because many viruses use iron to replicate themselves, large iron buildups may form leading to potential neurodegeneration (Fig. 1) [51]. Like many RNA viruses including most coronaviruses, the replication of the SARS-CoV-2 virus is dependent on manganese and iron, so it is possible that contracting COVID-19 may lead to the future onset of PD [52]. In addition, it has been found that heavy metals are found at higher concentrations in hepatitis C–infected individuals [53]. Therefore, people that contract RNA viral infections that are dependent on heavy metals should be aware of the potential risk of developing PD in the future.

COVID-19 and the Braak Hypothesis

The Braak hypothesis states that sporadic PD originates in the gut and the nasal cavity where a pathogen travels along the vagus nerve and olfactory tract toward the brain [54, 55]. The Braak hypothesis is supported by longitudinal clinical data which demonstrate that loss of smell and gastrointestinal dysfunction represent early PD symptoms, often preceding a definite PD diagnosis once motor symptoms present themselves [3, 56–59]. Further, due to evidence of LB formation in the olfactory epithelium [60, 61] and the enteric nervous system [62, 63], a-syn aggregation has been implicated as the pathogen referenced in the Braak hypothesis. That the staging presented by the Braak hypothesis resembles in many cases that of COVID-19 symptom progression is cause for concern. In essence, the Braak hypothesis describes a mode of pathogen transmission, likely a-syn

aggregates, which can bypass the blood–brain barrier and originate in two areas that are indeed affected by COVID-19.

Viral Infections, the Gut, and PD

The human body is inhabited by a diverse microflora which plays a role in many physiological and metabolic processes [64]. A healthy commensal microbiota plays a role in the breakdown of dietary substances that are too large to be digested and it has been shown to be essential for protecting the host against a variety of pathogenic infections [65]. Viral infections are among some of the most common invading pathogens that effect the host microbiota. In fact, our gut flora regulates viral expression yielding beneficial outcomes; however, it can also be regulated by viruses causing dysbiosis and a multitude of gastrointestinal (GI) issues [66]. The gut microbiota is decreased in older adults due to a number of factors that include diet, environmental factors, and genetics, and the rate and duration of viral infections are much higher in those with a compromised gut flora [67]. Patients with PD display an array of GI complications such as dysbiosis, constipation, and dysphasia (Table 1) [68], and these complications can occur up to 10 years before hallmark motor symptoms occur suggesting a possible link between the gut and the progression of PD (Fig. 2) [69]. Indeed, individuals with PD are at a higher risk of infection due to a compromised gut microbiota as well as severity of infections and emerging evidence has suggested that a rich and microbiota can play an essential role in modulating host immune response [70]. This occurs by stimulating the production of various pro-inflammatory cytokines during infection (Fig. 2).

Commensal microbiota has also been shown to directly suppress viral infections especially in certain sites where viruses can gain entry into the host [66]. Supporting this notion is the fact that *Enterococcus faecium* can prevent infection by the influenza virus by direct absorption and trapping as well as producing various metabolites to prevent viral infection [71]. Studies have also shown that microbiota depletion, due to antibiotic treatment, can result in significantly higher viral shedding [72]. Similarly, a study found that fecal microbiota transplants in rhesus macaques infected with simian immunodeficiency virus (SIV) induced greater antiviral immunity [73]. The immune gut homeostasis is delicately orchestrated by the fine tuning of the regulatory balance of pro-inflammatory responses, such as Th17, versus inflammatory regulatory T cells (Tregs) (Fig. 2) [73]. For example, gut probiotics like *Lactobacillus paracasei* increase pro-inflammatory cytokines like IL-33, IL-β, IL-12, and INFγ during influenza virus infection [74]. Quite a few studies have also shown that viral infections such as HCV/HBV can cause a profound alteration in gut microbiota causing dysbiosis, and this reduced gut diversity caused an increase in severity of infections [75]. A healthy gut microbiome is therefore essential in maintaining an optimal immune system to fight off pathogenic infections including viral infections.

It has been noted that severe viral infections could possibly increase the risk of developing PD later in life [76]. Clearly, viral infections are not the primary cause of PD but may act as vital triggers as alluded to previously in this review [77]. For example, it is known that virions can pass the blood–brain barrier and elicit inflammatory responses in the brain such as those observed in encephalitis [77]. It has also been documented that individuals

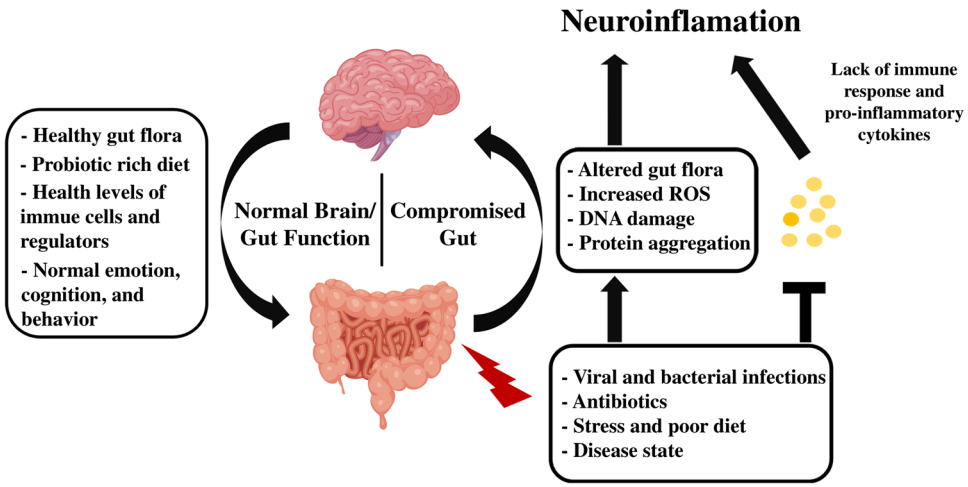

Fig. 2 The brain–gut microbiota axis: Schematic diagram highlighting the relationship between the brain and gut microbiota. A rich and diverse microflora allows for healthy immune and regulatory mediators, whereby a compromised gut microflora caused by viral infections, stress, antibiotics, and poor diet can cause a lack in immune response contributing to abnormal production of inflammatory cytokines which can lead to neuroinflammation

infected with hepatitis C are 30% more likely to develop PD than individuals who never had the virus [78]. Similarly, PD patients show a statistically higher antibody titer against the HSV-1 virus than healthy controls, and this autoimmunity has been further highlighted in mechanisms of a-syn molecular mimicry [79]. Indeed, the immunological cross-reactivity between HSV-1 and a-syn has been shown to cause destruction of dopaminergic neurons of the substantia nigra [80]. In many cases, SARS-CoV-2 primarily affects lung function through binding to ACE2 receptors present on the alveolar epithelial cells [81]. However, evidence has suggested that SARS-CoV-2 RNA can be detected in the stool of some patients with COVID-19 [82]. A recent study obtained blood and stool records from 100 patients with confirmed COVID-19, and 27 out of the 100 stool samples were collected 30 days after infection. The study discovered that the gut microbiome was significantly altered in patients with COVID-19 compared to control patients [83], showing a decrease in *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and bifidobacteria. Furthermore, the study showed elevated levels of C reactive protein and lactate dehydrogenase, and it was suggested that altered gut microbiota is involved in COVID-19 severity and this dysbiosis is observed after the infection has passed.

These data suggest that there may be a link between the gut microbiota and COVID-19 severity, particularly as the higher COVID-19 mortality rate is seen within the elderly population that have a decreased gut microbiota. Interestingly, PD patients with chronic GI conditions suffer from a decrease in gut flora causing constant bacterial infections [84]. This may suggest an increased chance of COVID-19 mortality for a patient with PD.

The Olfactory Tract

Loss of smell is one of the earliest symptoms of PD and the olfactory epithelium (OE) is becoming a target tissue to study PD and brain aging in general (Table 1) [2, 3, 85–87]. Indeed, olfactory dysfunction is as common as the other cardinal motor symptoms in PD and more prevalent than resting tremor [88]. Idiopathic hyposmia has been associated with an increased risk for PD in first-degree relatives of PD individuals [85, 89], and it has been suggested that neurologists should screen high-risk patients with olfactory tests [90].

Like PD, olfactory dysfunction is one of the earliest symptoms of COVID-19 infection and is therefore a key diagnostic criteria (Table 1) [91, 92]. With inhalation of SARS-CoV-2, the primary mode of infection, the nasal cavity and olfactory epithelium represent important targets for the virus. ACE2, critical to SARS-CoV-2 entry into cells, is expressed in sustentacular cells and basal cells of the olfactory epithelium, but is absent in olfactory sensory neurons [93]. Sustentacular cells act as support cells which provide major physical, metabolic, secretory, and absorptive support functions for the olfactory sensory neurons (OSN) [94] while basal cells of the OE act as stem cells producing OSNs since their lifespan is only a few weeks [94]. There are two mechanisms that could be at play here. First, RNA viral infection has been previously shown to be capable of inducing a-syn seeding in neurons [95]. Due to the prion-like activity of a-syn aggregates, a seeding event in any cell type of the OE can cause the propagation of aggregation throughout the OE toward the brain. Another mechanism of PD pathogenesis could be that the sustentacular cells and basal cells cannot function normally after infection and cause alterations in the OSNs. In fact, glial cell loss-of-function or gain-of-toxic-function has been thought to participate in the pathogenesis of PD [96]. A variety of PD risk factors are associated with altered proteostasis and metabolism in neurons and a single seeding event, be it caused by viral infection or disrupted homeostasis, could contribute to the pathology established in the Braak hypothesis [97].

PD Non-Motor Symptoms and COVID-19

One of the most common non-motor symptoms of PD is depression and typically, 30–40% of PD patients experience some form of depression in their lifetime post diagnosis [98]. It has been hypothesized that increased stress and a loss of emotional control are a result of a lack of dopamine-dependent adaptation [98]. In times of crisis, such as during the COVID-19 pandemic, stress-induced depression and anxiety may increase as a result of medical, financial, and social factors. For PD patients who have contracted the SARS-CoV-2 virus, it has been found that there is an increase in non-motor symptoms including trouble sleeping, mood changes, cognitive changes, and autonomic problems which all have ties to depression [99]. However, not only PD patients have experienced an increase in depression as a result of the pandemic. Factors including a lack of knowledge of infectious diseases, the effects of quarantine, inadaptability, and the fear for one's health all affect one's mental health whether that person has been infected or not [100].

COVID-19 and PD Guidelines

During the COVID-19 pandemic, numerous guidelines have been published in order to keep the world's populations safe and healthy. For many patients with PD, these guidelines are of course generally identical including the practice of social distancing and self-isolation if infected in order to prevent any further spread of the virus [101]. However, it has been noted that people with PD should remain active and engage in different forms of physical activity, particularly while spending time at home [102].

With regards to contagion, there does not seem to be a correlation between PD and contraction of the SARS-CoV-2 virus. However, if a PD patient does contract COVID-19, several complications may arise. It has been noted that PD patients are at larger risk of developing pneumonia and other respiratory infection, so clearly a SARS-CoV-2 infection may in many cases lead to a worsening of PD symptoms [101]. Indeed, urinary tract infections, pneumonia, or the flu can temporarily worsen PD symptoms, and it is therefore important for patients to have their PD medications readily available.

As with any underlying conditions, PD patients should consult with their physician in order to ensure that their PD medications are compatible with medications used to treat symptoms of COVID-19. It should be noted that certain cold and flu medications should not be administered together with, for example, MAO-B inhibitors, such as Azilect/rasagiline or Xadago/safinamide, frequently used to treat PD symptoms [101].

In the past few years, it has been noted that the number of PD cases has been on the rise. Although this rise in cases may be in part be attributed to an increasingly aging population, it is also believed that external factors such as pesticides, smoking, and viral infections may contribute to the increase [103].

Concluding Remarks

The global COVID-19 health crisis has challenged the way of life across the planet, affecting the economy, social interactions, and our health and safety. In this review, we have highlighted the intersections between PD, viral infections, and COVID-19 with an emphasis on the many similarities between RNA viral pathways and neurodegeneration in PD. Indeed, the onset and progression of PD, as detailed in the Braak hypothesis, as well as the pathogenic nature, molecular mechanisms, and symptom development of the disorder share many similarities with the SARS-CoV-2 virus and COVID-19. As further research is conducted, more evidence of a possible correlation between PD, viral infections, and the current SARS-CoV-2 virus will become available.

Authors' Contributions All authors contributed equally.

Data Availability All data are available and can be shared.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflicts of Interest The authors declare no competing interests.

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