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# SARS-Cov-2: The effects of COVID-19 on Parkinson's Disease and the Gut Microbiome

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## Abstract

Anosmia, encephalopathy, and seizures are some of the more severe symptoms of COVID-19 which is caused by SARS-Cov-2; COVID-19 has an important impact on Parkinson's Disease as well as other neurodegenerative diseases. There is evidence that coronaviruses are neurotrophic and SARS-Cov-2 was present in the brain tissue and CSF in autopsies of people who ultimately died of COVID-19. There is a measurable increased in pro-inflammatory cytokines, called a cytokine storm, from patients with COVID-19 that leads to potential immunologic changes to gut endothelium as well as dysfunction of the blood brain barrier. A pro-inflammatory state follows closely with α-synuclein dysfunction and accumulation as Lewy bodies which helps the development and progression of neurodegeneration diseases like Parkinson's Disease. Some viral infections, and other possible factors like genetics and organophosphate insecticides, or other unknown causes may be linked to increases in α-synuclein dysfunction or dopaminergic loss of neurons in the substantia nigra which are both delineated traits of Parkinson's Disease.

## Background

So far, there have been over 110 million diagnosed cases and 2.5 million deaths worldwide of SARS-Cov-2 (COVID-19) which has unequivocally pervaded our everyday lives. Most who contract COVID-19 have mild symptoms such as cough, sneeze, or headache/body ache, however, there are some who die, or end up having long lasting effects on their brain, heart, lungs, or other vital organs. With disease being spread typically through a sneeze, cough, or virion particles left on surfaces for a short time, COVID-19 follows the typical disease progression like SARS, MERS, or the seasonal flu. It may be possible that COVID-19 becomes another seasonal type of disease similar to the flu that we must take caution against every year. Cold weather and close proximity to others can contribute to the spread of respiratory diseases like COVID-19 and influenza. Early COVID-19 data suggests that some of the most at-risk people to catch COVID-19 are people over the age of 65, people suffering from chronic lung or cardiovascular diseases, immunosuppressed patients, patients receiving organ transplants, overweight/obese, or currently require medical treatments like chemotherapy or dialysis. SARS-Cov-2 was able to spread worldwide quickly while SARS and MERS were local epidemics. SARS and MERS should have served as a warning at how easily these coronaviridae viruses can spread yet were brushed off in the early 2000s. SARS-Cov-2 is considered to be the first pandemic of the modern world. The one major positive of a modern pandemic is the speed at which a new vaccine can be synthesized in such a short timeframe, the whole world seemingly joined forces to fight a common enemy. The only major concern regarding the vaccine is how long the vaccine will protect a host once inoculated. Current evidence has yet to prove the

longevity of the vaccines but scientists are hopeful that SARS-Cov-2 does not turn into a seasonal disease with new vaccine modifications every year like the flu.

Exploration of the potential relationships of SARS-Cov-2 and PD is essential in figuring out the physiological and pathological effects both diseases have on the body. My paper attempts to explicate hypothetical links of SARS-Cov-2 on the brain, lungs, and gut microbiome that relate to PD.

COVID-19 is considered to be a respiratory virus that presents itself as pneumonia-like symptoms with mild to severe symptoms including fever, cough, sneeze, and chest pain. One distinct feature of COVID-19 is abnormal symptoms like muscle soreness and gastrointestinal problems/disease (GI). The GI symptoms include but are not limited to diarrhea, vomiting, abdominal pain/discomfort, and changes to their gut microbiome. COVID-19 infects host cells through the angiotensin converting enzyme (ACE2) which acts as a receptor for SARS-Cov-2 to attach and infect host cells. ACE2 is prevalent in cells lining the lungs, heart, GI tract, and brain. The prevalence of ACE2 in cells in the GI tract suggest an alternative route for COVID-19 to infect beyond just respiratory lung cells. The gut-lung axis is an important crosstalk which can open the door to concomitant infection of both respiratory and GI cells. Therefore, if the lung tissue becomes infected with COVID-19 then the infection can maneuver its way down to the gut lining and impact gut microbiota by changing the microbiota composition. Infected tissue with COVID-19 can release a "cytokine storm" which may lead to damaging other surrounding tissues, which will be discussed more below. Recent studies have stated that a change of diet can lead to a change in the gut microbiota which can lead to an increase in immune responses and general homeostasis (Westfall 2017, Carabotti 2015). A positive diet full of probiotics and healthy balances of carbohydrates, fats, and proteins (and vitamins and minerals) can lead to a more effective immune response. A poor diet high in sugars or fats can disrupt the overall homeostasis of the gut microbiome rendering the local immune system inadequate, leading to increased host susceptibility to COVID-19. The gut-lung axis supports the idea that having a healthy, moderate diet and adding probiotics could help increase protective measures against respiratory diseases like pneumonia, bronchitis and COVID-19.

Additional axes like the gut-brain axis and the brain-lung axis further supports the importance of the health of the gut. Changes to the gut microbiota through diet changes or disease can impact the lungs, heart, and brain and might lead to permanent changes to those organs in the future. If, for example, COVID-19 particles end up getting swallowed and end up inside the gut, COVID-19 can proliferate and infect GI cells which may impact either the gut-lung axis or the gut-brain axis. Another possibility is if COVID-19 particles get inhaled and end up in the lungs and proliferate, then it is possible for COVID-19 to impact the gut-lung axis and the brain-lung axis. A third option is for COVID-19 particles to go straight into olfactory receptors in the nasal cavity and end up directly in the olfactory bulbs; from there, COVID-19 can make its way throughout other parts of the brain and cause inflammation like encephalopathy or neurodegenerative diseases, like Parkinson's disease. Early COVID-19 studies found patients with abnormal symptoms, for a respiratory disease, including gastrointestinal issues, abnormal liver function, and encephalitis. These are not indicative warning signs of PD, but these

symptoms may lead to inflammation elsewhere which will then lead to neuroinflammation and subsequently PD. As it stands right now, there haven't been any clear, direct linkages of COVID-19 causing PD but there may be suspected correlations in the future when more data arises.

**Parkinson's Disease**

Parkinson's disease (PD) is the second most common neurodegenerative disease behind Alzheimer's disease, yet it is the most rapidly growing neurodegenerative disease with an annual increase in 60,000 Americans or a total of approximately seven to ten million people worldwide are diagnosed with Parkinson's disease (Balestrino 2020). The greatest distinguishing hallmarks of Parkinson's Disease are the loss of dopaminergic neurons in the substantia nigra (SN) and an increase in misfolded α-synuclein (Balestrino 2020, Stefanis 2012). Lewy Bodies refer to a mixture of more than 90 molecules but a majority is comprised of PD-linked genes like GBA, α-synuclein, parkin, or DJ-1 (Wakabayashi 2013). While most people first show signs of PD in their sixties, about five to ten percent of people can have early onset symptoms starting in their fifties. Age seems to be the largest contributor to PD, but pathogenesis of unrelated diseases may contribute somewhat to PD along with gut microbiome changes. Based on microbiota studies, PD patients have been shown to have an increase in bacteria from genera *Akkermansia, Bifidobacterium,* and *Lactobacillus,* and a decrease of *Blautia, Faecalibacterium,* and *Prevotella* (Scheperjans 2018). One major debate in the pathogenesis of PD is if the gut microbiome changes precede disease onset or are the cause of disease progression.

Parkinson's Disease, though non-infectious, exhibits characteristics of a pandemic (Dorsey 2018, Dorsey ER 2018). The amount of people who have been diagnosed with PD have doubled from 1990 to 2015 and are expected to double yet again from 6.9 million people in 2015 to approximately 14.2 million people in 2040 (Dorsey ER 2018). The exponential increase in PD patients is mostly due to aging but can also be attributed to industrialization (Dorsey 2018). This increase in ageing of the world follows the basic idea that as the population ages, the prevalence of neurodegenerative disorders associated with older age, like PD, increases. In one neurological projection, the increased burden of such neurodegenerative disease may have started to affect the younger population increasing diagnoses of migraines, epilepsy, and multiple sclerosis (Albert 2007, GBD 2016).

Though not entirely linked, migraines and headaches are common symptoms of PD patients. Although the intensity or frequency were not associated with different stages of PD; an increase in migraines among the younger generation may cause concern for future neurodegenerative disease progression later in life (Sampaio 2020). Having neurological changes or brief inflammation may have some correlative effects later in life, though no data has been proved. A correlation between migraines, epilepsy, multiple sclerosis and neurodegenerative diseases has yet to be proven as, currently there is not much evidence as of yet. There have been many factors that can contribute to correlating with PD and some of those

include Dichlorodiphenyltrichloroethane (DDT), Dieldrin, and genetic mutations like mutations to the SNCA, GBA or PARK2 genes.

**Genetics Associated with PD**

Parkinson's disease is largely attributed as a genetic disease and there are currently over 90 independent risk variants associated with helping to lead to PD. One of the most common risk factors for Parkinson's Disease or Lewy body dementia is variation in GBA which codes for glucocerebrosidase, which is important for cleavage of the glycolipid glucosylceramide (GlcCer). Variation to GBA, which encodes glucocerebrosidase, can lead to Gaucher disease, an autosomal recessive lysosomal storage disorder, and is believed to contribute to a reduction in ability to degrade α-synuclein. The lack of α-synuclein degradation could then contribute to an increase in Lewy bodies which is an important hallmark in PD patients. GBA has been an important target for therapeutic development lately, and the estimated completion of one study is May 2021 (ClinicalTrials.gov Identifier: NCT02906020) (Blauwendraat 2020). The α-synuclein gene (SNCA) has been shown to be a direct linkage to causing PD and one major piece of evidence for this is the fact that mutation of the 53$^{rd}$ amino acid, from alanine to threonine, (in Italian and Greek heritage families) and mutations in the 30$^{th}$ (alanine to proline) and 46$^{th}$ (glutamine to lysine) amino acids in Greek and Spanish families shows considerable change to the N-terminal domain of the protein. This change to the N-terminal domain leads to changes in how the protein aggregates together (Guhathakurta 2017). The familial heritage gene mutations linked with deregulation of α-synuclein expression helps lead to explaining that PD can be at least a genetically transmittible disease. There are other factors like oxidative stress and organophosphate insecticides that could potentially cause PD as well.

**Organophosphates linked with PD**

Dichlorodiphenyltrichloroethane (DDT) is an odorless, tasteless organophosphate originally created as an insecticide in 1874 by Austrian chemist Othmar Zeidler. Some adverse by-products of industrialization, like DDT or other insecticides, may be participating in the increase in Parkinson's Disease (Richardson 2019, Goldman 2013). One specific pesticide, DDT, was banned in the United States in 1972 over its environmental persistence, with a half-life of about ten to fifteen years in soil yet was not linked to overt toxicity or neurotoxicity (CUETO 1956, Morgan 1971, Misra 1984). After 1972, there was no overt studies done on the impact of DDT and PD, nor was there any significant drop in diagnoses due to banning of DDT (Blauwendraat 2020). The potential long-term exposure of DDT on humans has never been explicitly studied, however, two studies found that workers engaged in spraying DDT were found to have cognitive dysfunction, though no amounts of DDT or its metabolite Dichlorodiphenyldichloroethylene (DDE) were recorded (van Wendel de Joode 2001, Fleming 1994). One study had found DDT in post-mortem brains of Alzheimer's patients more often than in brains of patients with PD but a lipid-soluble, long-lasting mitochondrial poison, dieldrin, was found in Parkinson brains more than Alzheimer's brains (Jorgenson 2001). No conclusions

have been made as to why DDT ends up in more Alzheimer patients than PD patients or that dieldrin ends up in more PD patients than Alzheimer patient's post mortem results. Dieldrin is another type of organochloropesticide that has been linked with Parkinson's disease.

Dieldrin has an extremely long half-life of anywhere between 141 to 592 days and may persist in soil sediments and human serum of those previously exposed (Richardson 2019, Jorgenson 2001, Weisskopf 2010, Richardson 2009). According to Weisskopf, and colleagues, increasing the concentration of dieldrin was associated with an increase in the odds of Parkinson's Disease (Weisskopf 2010). In vitro studies using dopaminergic neurons exposed to dieldrin have been shown to promote mitochondrial oxidative stress and eventual mitochondrial dysfunction which will ultimately lead to apoptosis (Richardson 2019, Kanthasamy 2008, Kanthasamy 2005). This is an important distinction because PD's hallmark trait is dysfunction or loss of dopaminergic neurons in the substantia nigra (SN) and this study shows the direct correlation between neurons exposed to dieldrin and an eventual cell death via apoptosis. Studies about dieldrin induced neurotoxicity have been studied heavily in mouse models. One major concern was having neurons exposed during significant developmental stages (typically in utero) may be more vulnerable to chronic oxidative stress later in life (Richardson 2006).

**Gut Microbiome**

The human gut microbiota consists of approximately $10^{14}$ microorganisms and is made up primarily by bacteria, archaea, virus, protozoans, and fungi with two distinct bacterial phyla making up three fourths of the entire gut microbiome, *Firmicutes* and *Bacteroides* (Carabotti 2015). The gut microbiome has been an increasingly studied field lately as more studies find more possible links to the gut microbiome. The gut microbiome has connections like the gut-brain axis and the gut-lung axis which are important in PD studies and the ever-increasing worry about the effects of COVID-19 on the gut, brain, lungs, and heart.

Bacterial infections can be fought with antibiotics, but antibiotics can also kill good bacteria in the gut wall making it possible for pathogenic bacteria to take root and proliferate instead. The loss of good bacteria from the gut can be combated with prebiotics, probiotics, and a transfer of bacterial ecosystems through fecal transplants. Since COVID-19 is a viral infection, antibiotics will not help, however, if a patient had a bacterial infection and had taken antibiotics before contracting COVID-19, the results could likely be more harmful due to changes in gut microbiota. This drug interaction could be entirely independent and a simple correlation between gut microbiome changes and pathogenesis of PD, however, the gut microbiome is a key regulator in neuroinflammation by affecting microglia activity (Erny 2015). Furthermore, gut microbiota affects local environment in the gut lumen which could have an impact on environmental toxins and other PD causing factors.

The human gut microbiota mostly stays the same after the first three years of life, however, it has the capability to change slightly due to the host's diet or to other environmental factors like diseases or antibiotics. There are associated diseases due to alteration in gut microbiota like colorectal cancer, obesity, inflammatory bowel disease and type 2 diabetes

(Angelucci 2019). The gut microbiome connects to the host epigenome via signaling methods, and metabolites, caused by changes in gut environment or after nutrients get absorbed and end up crossing the blood brain barrier. One major signaling network is the "gut-brain axis" which connects the gut microbiome to the central nervous system by releasing hormones and/or cytokines to react with neurons for subsequent actions (Westfall 2017). The vagus nerve is an important pathway that sends and receives nerve impulses to or from the gut and brain via afferent and efferent nerve fibers. This is a direct connection between the central nervous system (CNS) and the enteric nervous system (ENS) which impacts cytokines and hormones from being released. Additionally, the enteric nervous system can interact with the central nervous system by the gut bacteria (Carabotti 2015). The ENS can also affect the CNS by sending long axons in the myenteric or submucosal plexus, or by sympathetic or parasympathetic axonal input to and from the brain. This entry point into the body can not only have pathogens enter, but also a therapeutic benefit by studying pharmacokinetics and pharmacodynamics of how drugs are metabolized by the gut and processed by the liver and kidneys. This oral entry could be a starting point to combat infections by utilizing antibiotics or antivirals instead of vaccines through intramuscular injection.

**SARS-Cov-2**

SARS-Cov-2 (COVID-19) is the current pandemic and as of February 2021 there have been nearly 110 million global cases and nearly 2.5 million deaths, according to Johns Hopkins Coronavirus Research Center. SARS-Cov-2 is a type of positive sense RNA stranded coronavirus that belongs to the betacoronavirus 2B lineage (Lai 2020). The Coronaviridea family can be divided into the sub-family called Orthocoronavirinae which can be broken down into: Alphacoronavirus, Betacoronavirus, Deltacoronavirus, Gammacoronavirus, and a lesser known unclassified Orthocoronavirinae. The Betacoronavirus subfamily can be broken into subgroups A, B, C, and D. Subgroup B is where SARS, SARS-Cov-2, and MERS are classified (Tezer 2020). This virus subgroup acts similarly, are transmissibly similar, and have similar hosts while having human carriers.

Among the similarities between the SARS outbreak in the early 2000s and SARS-Cov-2 outbreak in 2019, some of the major differences between these two coronaviridae viruses are where they emanated from and their possible intermediate hosts. These viruses both have bats as their natural reservoir hosts, but their intermediate hosts could be pangolins for SARS-Cov-2, and civet cats for SARS. Another important distinction between these two viruses is how each virus was able to spread and to how many people one infected person can potentially infect. The $R_0$ value for each virus is similarly around 1.0 – 4.0 (D'Arienzo 2020, Caldaria 2020). Since the $R_0$ value is similar, the other question to ask is about asymptomatic spread of the viruses. The asymptomatic spread of COVID-19 has been predicted to have been higher than SARS, however, the degree of asymptomatic transmission isn't fully understood but the immunogenicity of SARS-Cov-2 may be more impactful than SARS.

**Immunogenicity of SARS-Cov-2**

The structure and binding of SARS and COVID-19 has been shown to use the same receptor, Angiotensin Converting Enzyme 2 (ACE2). The spike (S) glycoprotein gets cleaved into S1 and S2 subunits. The S1 subunit gets further divided into an N-terminal domain (NTD) and a C-terminal domain (CTD) which are part of the receptor binding domain (Lu 2019). Wang et. Al. states that SARS-Cov and MERS-Cov use the S1 CTD domain to recognize the receptor (receptor binding domain (RBD)). Wang et. al conducted an experiment to figure out how SARS-Cov-2 spike domain interacts with the receptor. They had found, using immunostaining and flow cytometry assays, that the S1 CTD region is the key region for interaction with hACE2 receptor. The crystal structure produced by the SARS-Cov-2-CTD region and hACE2 receptor produced a binding similar to that found in SARS-Cov-RBD. Their data, however, shows that SARS-Cov-2-CTD has a higher affinity for binding than SARS-Cov-RBD which shows difference between the two viruses and their interactions with the same ACE2 receptor. Another test using monoclonal antibodies against SARS-Cov-RBD was unable to bind and react with SARS-Cov-2 S protein which indicates a difference in antigenicity. The use of a vaccine against SARS will have no effect against COVID-19, however, it may give ideas for creating a vaccine based on the SARS vaccine.

Once SARS-Cov-2 interacts with the ACE2 receptor the viral particles can begin its entry into the host cells. When the SARS-Cov-2 genome gets inside the host cell, it will use the host cell's genomic transcription and translational machinery to make more copies of the viral genome which is approximately 29.9 kb in length (Lu 2019). Of the 29.9 kb genome, SARS-Cov-2 contains four structural proteins (spike protein, envelope protein, membrane protein, nucleocapsid protein) and sixteen non-structural proteins (Wang 2020). The viral genome is then packaged into vesicles and then exocytosed from the nucleus into the cytoplasm of the host cell. The host cell can continue to create new virion structures until the cell bursts and those virions can now infect other host cells. This perpetual cycle of infection, replication, and bursting will eventually be recognized by cytokines and kickstart the immune response.

Antigens are any foreign molecule that, when recognized by the body, will promote cytokines to tag the antigen and start the immune response. It has been shown to be possible that a SARS-Cov-2 viral infection can produce an excessive immune response called a cytokine storm (Tezer 2020). This cytokine storm is triggered by interleukin 6 (IL-6) and can affect a broad range of cells and tissues and end up causing acute systemic inflammatory syndrome or acute respiratory distress syndrome (ARDS). According to Tezer, a report in The Lancet stated that the most common cause of death in COVID-19 patients is ARDS. The cytokine storm that is produced from COVID-19 can cause ARDS along with multiple organ failure and an eventual death. Some of the most common organs that are impacted by COVID-19 are the heart and lungs; however, the connections between the lungs, heart, gut microbiome, and brain, makes it possible that once one organ gets infected the rest may follow.

**Neuroinvasive potential of SARS-Cov-2**

One possible way that COVID-19 can enter the body is through the mouth and make its way into the stomach and eventually the GI tract. This can be due to changes in the GI microbiome that lead to changes in the brain via the gut-brain axis. The gut-brain axis is a bi-directional communication point between the CNS and the ENS which can lead to cognitive changes due to gut pathogens. Some of the most prevalent data about the impact of the gut-brain axis is about encephalopathies along with irritable bowel syndrome (IBS), and even studies about possible regression of autism spectrum children with high levels of antibiotic prescriptions at early ages. These studies relate broad spectrum antibiotics to deal with possible diseases like chronic diarrhea in young children, with then colonization of potentially more neurotoxin producing bacteria which led to autism like symptoms (Sandler 2000). Sandler et. al. treated the autism spectrum children with vancomycin to specifically target *Clostridia* bacteria, which has been shown to be increased in autistic patient's gut microbiomes, which led to a slight regression in behavioral symptoms. The CNS has been shown to release anti-inflammatory responses to the gut microbiome to regulate possible pathogens within. Since the gut-brain axis can have significant changes due to changes in pathogens of the gut microbiota, it can be suggested that one way that SARS-Cov-2 might enter the brain is via the gut-brain axis after entering through the gut microbiome. Another possible way is through the gut-lung axis which if you have COVID-19 affecting the lungs, it could affect the gut and subsequently the brain as well (Lai 2020).

COVID-19 can also enter the body through the nasal cavity, via the olfactory receptors in the cribriform plate. After entering the olfactory receptors, COVID-19 can enter the olfactory bulbs within the brain. The olfactory bulbs, located on the ventral aspect of the frontal lobes, are responsible for smell. The olfactory bulbs send axons to the thalamus to process smells; the thalamus also processes taste from taste bud receptors from the tongue from five taste modalities: sour, sweet, bitter, salty, and umami. It has been shown that the COVID-19 virus can enter the brain through the nasopharynx by exploiting the olfactory mucosa, endothelium, and sensory nerve cells (Meinhardt 2021). By entering through the nasal cavity, this may be the leading cause of why some patients experience anosmia, hyposmia, or ageusia. One study was conducted using 417 patients and found that 357 patients had olfactory dysfunction related to COVID-19 (Lechien 2020). The patients olfactory dysfunction occurred mostly after general ear, nose and throat (ENT) symptoms, and in 59 clinically cured patients, about 72.6% of patients had their olfactory function recovered mostly within a week after being deemed clinically cleared of COVID-19 (Lechien 2020). In the same study, 342 patients reported gustatory dysfunction, though 32 patients were not counted due to them not remembering any gustatory dysfunction. Of these patients, 78.9% and 21.1% had reduced/discontinued or distorted gustatory dysfunction to salty, sweet, bitter, or sour, respectively (Lechien 2020). Though not extensive, this study shows evidence of olfactory and gustatory dysfunction among COVID-19 patients.

**Heart and lung invasion of SARS-Cov-2**

The gut-lung axis is another bi-directional crosstalk which means that inflammation in lungs can affect the gut microbiome (Erny 2015). The lungs have been shown to have their own microbiota that is different than the gut microbiota which has been demonstrated by using bronchoalveolar lavage (BAL) fluid or tissue samples (Bingula 2017). Even though contamination of lung samples is possible, it has still been proven that the lung has its own microbiota and that the lower respiratory tract and the upper respiratory tract have distinct but related microbiomes (Goddard 2012). The upper respiratory tract consists of the oropharynx, laryngopharynx, nasal passages, paranasal sinus and part of the upper larynx whereas the lower respiratory tract consists of the lower larynx, trachea, bronchi, and alveoli (Man 2017). Each location within the lungs have physiological and microbial gradients. These gradients are important physiologically because certain aspects of gas exchange only occur in the lower respiratory tract while gas transport occurs in the upper respiratory tract. The same idea is similar in bacterial gradients. Some bacteria might not handle carbon dioxide as well as others or maybe warm, moist air might be harder to survive in. Since COVID-19 is a respiratory disease, it will most likely infect the lungs first and foremost before most other areas of infection. The inflammatory response to COVID-19 from the body may cause that cytokine storm previously mentioned and then cause inflammation elsewhere in the body and it might ultimately end up leading to the brain through the gut-brain axis.

**Conclusion**

The ongoing COVID-19 pandemic has already impacted a large number of people and it is associated with many disease symptoms. Although the acute behavior of COVID-19 seems to be relatively worked out, the chronic effects of COVID-19 are yet to be seen as chronic after effects have yet to happen. The systemic inflammatory response of SARS-Cov-2 seems to be amassed on neuroinflammation, but data so far is speculation. The effects of neuroinflammation associated with COVID-19 may be involved in neurodegeneration and links are through the gut, lungs, and directly through the olfactory bulbs. Also, if there is dysfunction of the blood brain barrier or gut epithelial layer more gut metabolites can pass through and end up into the CNS and cause microglial activation which impact neurons which ultimately leads to neuronal death along with potential cyclical α-synuclein dysfunction and more activated microglia.. With all of the presented information, I believe that there is a possible relationship between SARS-Cov-2 and the pathogenesis of PD. Thus, immediate vigilance may not be needed but long-term vigilance will be, especially if SARS-Cov-2 becomes a routine seasonal disease.

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