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A Metanalysis of Parkinson's Disease

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ABSTRACT

Parkinson's disease is one of the most prominent and devastating neurodegenerative disorders worldwide. However, each PD patient has a unique disease course due to individual variations in the rate of cognitive and psychomotor decline. In this review article, we will analyze factors influencing such individual variation and the amount of concrete information we currently have on PD. We will focus particularly on genetic factors, social/socioeconomic factors, and medical comorbidities using existing data and information gathered from previous experiments. We will discuss the implications such factors should have on treatment options and disease management and the effects the COVID-19 pandemic had on PD patients.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system that results in uncontrollable movements. Disease progression manifests as a gradual loss of coordination, balance, and talking. With a staggering 90,000 people in the United States diagnosed with PD each year and more than 10 million people worldwide living with PD, it is considered one of the most prominent and devastating neurodegenerative disorders society currently faces.[1] However, given that many individuals are either misdiagnosed or undiagnosed due to socioeconomic factors that will be discussed below, it is very likely that the prevalence of the disease is even higher.[1]

PD is incurable, mostly attributed to the unique and individualized nature of the disease. Symptoms of PD start to emerge due to a loss of dopaminergic neurons in the basal ganglia, a region in the brain that functions to promote smooth, coordinated movements and inhibit excessive movements.[2] This progressive loss or impairment of dopaminergic neurons significantly decreases the production of dopamine, a neurotransmitter responsible for various functions, such as feelings of pleasure, memory, and movement.[3]

Experts have gathered that factors such as genetic, environmental, and socioeconomic factors play a larger role than expected in influencing each PD patient's distinctive disease course. For example, recent evidence has revealed the impact of the COVID-19 pandemic on PD patients, which will be discussed in further detail. With ongoing medical advancements, we are hopeful to see continued progress made on possible treatment and disease management options for PD patients.

In the present work, we will review research that has elucidated genetic, environmental, COVID-19, and socioeconomic factors influencing PD prevalence and its disease course. We will also discuss the implications these factors have on PD treatment options.

Genetic Factors Influencing PD

Discovering genetic influences and factors of any disease, especially PD, is essential for those trying to understand its etiology. However, as previously mentioned, the disease course of PD patients is incredibly unique and individualized, with the rate and intensity with which cognitive and psychomotor problems develop varying

among patients. The exact mechanisms are likely to involve multiple genetic, neurobiological, and environmental factors. As a result, most evidence and data collected in an attempt to narrow down biological markers and genes, to name a few, are similarly varied and diverse. Despite these diverse results, many of these studies limit the pool to Caucasian populations, thus limiting other variations of genetic backgrounds from other races[4]. All in all, very little of what has been discovered about genetic influences and factors in PD is definitive.

For now, what we do know are different genes found to be associated with different factors of PD. Genes such as a-synuclein and catechol-O-methyltransferase [COMT] have been found to provide insights into the role dopaminergic systems have in developing cognitive impairment in Parkinson's disease[5]. Other genes like apolipoprotein E (APOE) and microtubule-associated protein tau (MAPT) are associated with dementia and found in similar neurodegenerative diseases, such as Alzheimer's disease and atypical Parkinsonian syndromes.[5]

A 2012 study based in Philadelphia, Pennsylvania[5] sought to determine the association of APOE, MAPT, and COMT with cognitive decline in PD using records of annual changes in Dementia Rating Scale-2 (DRS-2) scores and assessments of 212 subjects. The subjects were recruited and separated by genotype groups for APOE, MAPT, and COMT through DNA extraction from peripheral blood. Researchers concluded that the presence of the APOE e4 allele was associated with a significantly higher annual rate of decline in the Dementia Rating Scale-2 (DRS-2) score in comparison to subjects with other genotypes. Additionally, a Cox's proportional hazards regression analysis of the data demonstrated a 2.8-fold increased risk of a 10-point decline in the DRS-2 score. On the other hand, APOE e2, MAPT H1/H1genotype, and COMT Met/Met genotypes were not associated with significant changes in DRS-2 score overall. The COMT Met/Met genotype was only associated with higher attention subscale scores while the MAPT H1/H1 genotype was associated with lower scores in the memory subscale over the course of the study.

The results of the study made many distinctions concerning the effects of the APOE e4 allele, as carriers of the gene showed the most statistically strong changes. The study revealed that the effect of the APOE genotype on cognitive decline was also associated with a decline in all DRS-2 subscales (initiation, construction, conceptualization, and memory), excluding attention. Altogether, the findings suggest a small association between APOE and the cognitive decline of PD. However, a possible weakness the study notes is that other cross-sectional analyses have failed to find data to support APOE e4 effects on PD, referencing a past study from Cambridge.[6] Additionally, this particular Cambridge study not only failed to find data to support APOE e4 effects but also failed to observe any association between cognitive decline and the e2 allele, in contrast to other studies that have found it to be associated with increased incidence of PD. These diverse results only further undermine any evidence that certain genes are directly associated with cognitive decline.

DRS-2 Domain	Estimated *APOE* ε4-Associated Annual Change	95% CI	*P* Value
Initiation	−1.1	(−1.7, −0.48)	<0.001
Attention	−0.1	(−0.43, 0.22)	0.53
Construction	−0.21	(−0.58, −0.35)	0.006
Conceptualization	−0.7	(−1.1, −0.26)	0.002
Memory	−0.84	(−1.3, 0.41)	<0.001

Figure 1. Association Between APOE e4 and Annual Change in DRS-2 Domain Subscores, from Morley et al., 2012.

Commonly detected genetic variants also seem to differ based on location, as research has found that the PRKN gene is the most frequently detected causative gene in Japan. It is the causative gene of autosomal recessive juvenile PD and has been identified in over 2000 cases.[4] A study of the PRKN gene identified biallelic

variants in PRKN in 8.1% of familial PD cases and 5.8% of sporadic PD cases. The age of onset of those with the biallelic variant(confirmed to have the gene) of the PRKN gene reportedly was 29.6±9.8 years and 45.2±15.9 years for those with the monoallelic variant(those that were carriers), essentially going against a widely accepted notion that PD incidence increases with age, typically in the 65+ range.[1] In addition, patients with stage 4/5 in the Hoehn & Yahr Scale[7] were identified with biallelic variants of PRKN who had PD for at least 15 years. Stage 4 in the Hoehn and Yahr Scale is defined by patients with severe disabilities who are still able to somewhat stand or walk unassisted, while stage 5 is defined by patients wheelchair-bound or bedridden unless aided.[7] Those with the monoallelic variant are generally assumed to be unaffected carriers, but still have a somewhat higher frequency in Japanese PD patients than other genes, concluding that even the monoallelic variant has some influence on the onset of PD. The PRKN gene presents as potentially being the cause of much more severe and early symptoms of PD than compared to those in the U.S., again supporting how diverse the potential genetic factors involved with the pathogenesis of PD are. However, the more potential genes and their association with PD pathogenesis are researched, the more complete a hypothesis can be created.

The genetic influences on PD remain to be conclusively described and are an ongoing area of research. Genes such as APOE e4 and PRNK may play a role in PD development and/or rate of disease progression. It remains challenging to conclusively distinguish genetic factors from other influences on PD disease courses, including potential environmental exposures such as pesticides, herbicides, and heavy metals.

Environmental Factors Influencing PD

Along with genetic factors, Parkinson's disease pathogenesis is thought to have many other contributing factors, such as environmental factors. Simply put, environmental factors refer to exposures due to substances, job/housing locations, and behaviors/habits. These factors play a role in cases of PD that may be attributed to environmental exposure to neurotoxins. However, note that data for these claims are still inconsistent, as claims about the onset of PD usually are.

Data has shown the possible correlation between populated urban areas and an increased risk for PD since these urban areas have also been found to have connections between industrial heavy metal and air pollution from vehicles[8]. Rural exposures may also prove to be a risk as well, as certain occupations such as those in agriculture, involving working with pesticides or heavy metals, electrical vocations, etc. have been investigated as possible factors that contribute to the increased risk of PD[8]. The elevated incidents of PD discovered in rural areas may also be due to the higher number of aged population.[8]

Pesticides

Pesticides have been used globally in the agricultural industry and by public health authorities to control pests (insects, unwanted plants, etc) and disease vectors. In particular, the chemical compound, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), has been a point of interest due to its ability to target the substantia nigra[8], a brain region responsible for the production of dopamine and affects other systems in the nervous system, such as movement control, cognitive executive functions, etc[2]. Those exposed to MPTP presented textbook cases of advanced PD and unsurprisingly, these results led to the speculation of pesticides potentially having an association with parkinsonism.

Research from San Jose, California in 1982[9] that hypothesized MPTP started with the evaluation of a patient with an original diagnosis of catatonic schizophrenia. However, the patient was observed to have unusual symptoms, where he was unresponsive, yet seemingly alert with no spontaneous movement. He also exhibited "waxy flexibility", where the arm was involuntarily raised and stayed in the position for a prolonged period. It was discovered that the patient had a distinct feeling of irregular active resistance in line with PD and looked like a textbook case of PD. Six similarly affected cases were discovered and all seven patients displayed

all of the motor symptoms of PD and even non-motor symptoms (facial seborrhea, cognitive function deficiencies). All of the cases were linked to a new synthetic heroin that was composed of almost pure MPTP, therefore suggesting that MPTP was the likely cause of Parkinsonism in the patients. Research later discovered the MPTP itself was not toxic but metabolized by astrocytes in the brain to MPP+; MAO B was then found to be responsible for this biotransformation, an enzyme in the body that breaks down chemicals, such as dopamine, in the brain[10]. MPP+ was also found to have a similar composition to paraquat, a commonly used herbicide, differing by only one methyl group. These discoveries incited the idea that pesticide exposure may be related to PD pathogenesis and thus began continuous studies to investigate this possible relationship. Interestingly, in some studies, it seems as though the risk of pesticide exposure is largely elevated by the presence of certain genetic variants, while others claim that most PD cases are largely related to environmental factors[11]. Either way, MPTP has currently become the only environmental agent identified so far that is capable of inducing parkinsonism; a breakthrough in PD research as finding anything definitive or conclusive relating to PD is a huge rarity.

Insecticides now commonly investigated include organochlorines and organophosphates. For example, dieldrin is a popular organochlorine pesticide found to be associated with an elevated risk of PD because of its effects on the central nervous system and its targeting of the dopaminergic system[8]. Rotenone is another major organophosphate associated with the risk of PD for its acceleration of a-synuclein aggregation, which results in the death of dopaminergic neurons[8]. The severity of the impact of both pesticides is dose-dependent[8]. Again, note that the data for the correlation is still unclear, and many of these conclusions have been found using non-human models that only have a 60% correlation with human disease.

Heavy Metals

Claims of association of elevated risk of Parkinson's disease and heavy metals have differed among the studies aimed at analyzing this correlation. Numerous studies have denied any correlation between the two while other epidemiological studies have discovered an association between PD and single or mixed exposure. A meta-analysis from 2015 included five studies and 125,507 individuals to analyze specific metal intake and its associations with Parkinson's disease and concluded that dietary iron and an increased risk of PD had no significant correlation[12]. Another from 2016 aimed to assess the levels of copper, iron, and zinc in PD patients of different progressions concluded that serum concentrations of the metals did not have significant correlations with disease progression[13]. However, others have identified iron, manganese, mercury, lead, and copper as potential causes and contributors to PD[11]. We will analyze iron here as an example.

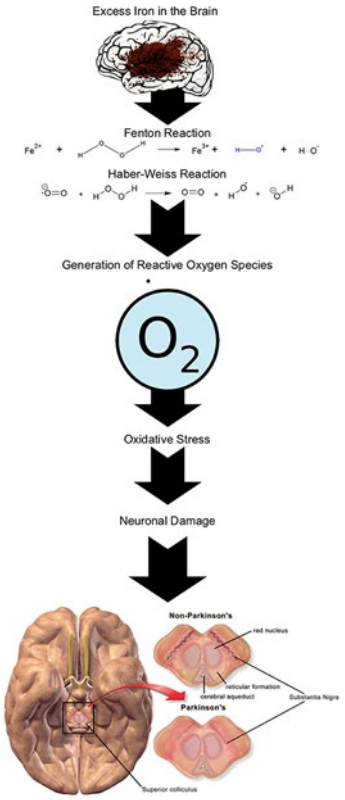

Figure 2. Fenton-Haber-Weiss reaction, from Ball et al., 2019(9). Process of excess iron leading to neuronal death.

Typically, a healthy brain has higher concentrations of iron in the substantia nigra and globus pallidus and lower concentrations in the midbrain, cerebellum, cortical gray matter, and white matter[11]. Therefore leads to the conclusion that regions of the brain involved with motor function have higher concentrations while the regions that aren't have lower concentrations. However, increased concentration of iron in the substantia nigra is neurotoxic, and PD patients have an especially high accumulation of iron in the brain[14]. The balance of iron concentration is crucial, as iron is also essential in dopamine synthesis due to its role as a cofactor for tyrosine hydroxylase, an enzyme that limits the production of chemical transmitters; an imbalance can have damaging effects on dopaminergic neurons. Other research has found that iron also plays a role in oxidative stress[8], a condition when antioxidant levels are too low to protect the body from free radicals, which leads to the break-down of cell tissue, DNA damage, and neuronal death[15]. More specifically, excess iron will lead to the Fenton-Haber-Weiss reaction, which causes the formation of hydroxide and hydroxyl radicals[16] while also generating reactive oxygen species that increase oxidative stress and eventually cause neuronal death. In general, chronic exposure to heavy metals triggers this free radical generation and decreases antioxidant levels, and not only leads to oxidative stress but also results in protein aggregation, a biological phenomenon in which mutant or damaged proteins bind together into a large mass[17]. Note that research has also shown that there is no significant link found between increased dietary intake of iron and PD risk, concluding that environmental factors are more likely to be the cause of any excess iron that might increase PD risk[8].

Analyzing potential environmental factors that may induce parkinsonism or are contributors to PD seemingly provides more concrete evidence and conclusions relative to other PD research that is far more varied and inconclusive. Therefore using such research on environmental factors can be used as a launching pad to

explain other results, such as in the case of socioeconomic factors that are far more general and can be explained by subfactors.

Impact of COVID-19

Despite the multitude of global consequences the pandemic left on the world, very little is known about the impact of public health policies implemented to combat COVID-19 on those with PD. There are a limited number of studies that show the pandemic's toll on the mental health and daily routines of people with PD; however, we can draw some conclusions on what factors could have affected those with PD.

Pandemic Impacts on Mental & Behavioral Changes

During the pandemic, everyone, including PD patients, was recommended to adhere to social distancing regulations, quarantine, and all public health guidance. However, these regulations were in direct contrast to pre-pandemic PD management which included increased socialization and physical activity. Socialization was especially important for decreasing negative mood symptoms in PD patients who were found to have stress-related psychiatric conditions like depression and anxiety, pre-pandemic[18]. Routine exercise is a well-established way for PD patients to help maintain strength, flexibility, balance, and cognitive acuity[20]. Exercise can also help reduce motor symptom progression. However, because of public health regulations, many outlets for PD management were restricted; such as gyms, community centers, etc. The limited number of studies available have reported resulting worsening stress, anxiety, and depression in PD patients. For example, a study hoping to research the impact of COVID-19 on the mental health, physical health, and quality of life of PD patients[18] found[19] that out of the 38 PD patients interviewed, using the DASS-10 scoring scale, the average DASS depression score was a high number of 7, the average DASS anxiety score was a 4, and the average DASS stress score was also a higher number of 7. In contrast, the control group, those that did not have PD, out of 20 people were found to have an average DASS depression score of 3, an average DASS anxiety score of 2, and an average DASS stress score of 4. A survey in a published study in the journal *Parkinson's Disease*, "Stress and mindfulness in Parkinson's Disease - A survey in 5,000 patients" revealed that stress worsened PD symptoms ranging from dyskinesia, freezing of gait(FoG), bradykinesia, etc.[21] Managing stress, anxiety, and depression is not just a matter of improving quality of life for PD patients, but also a factor of symptom severity. The combination of COVID-19-related stress and the limited resources to manage said stress undoubtedly could have led to increased severity of PD symptoms during the pandemic. Pandemic regulations also derailed routine pre-pandemic healthcare delivery. Usual in-person physician care, and physical, occupational, and speech therapy were, unsurprisingly, modified to follow social-distancing requirements. All in all, the pandemic may likely have indirectly affected PD patient treatment delivery, efficiency, and quality of life.

In a survey study[22] intended to analyze the impact of social-distancing regulations on PD patients, 45.9% of a group of 1,342 PD respondents reported some negative change in their symptoms during the pandemic. A factor that may have potentially resulted in this high number was the 59.9% of respondents that reported canceling a doctor's appointment during the pandemic, out of fear of "being infected myself"; a common concern voiced by more than 85% when asked about changes in their personal lives during the pandemic. However, note that it is not possible to confirm if these negative changes were the direct result of worsening mental health factors like depression and anxiety. 63.5% of the respondents also reported using telehealth during the pandemic for physician appointments, and many were satisfied with their telehealth visits compared to in-person visits. However, many essential PD treatments like physical and mental health therapy, speech and language pathology, and occupational therapy were less commonly used via telehealth, and the study observed that telehealth for these treatments lagged behind physicians' appointments. The study also found a correlation between telehealth and mental health, as PD patients who felt more depressed or hopeless were more likely to have used

telehealth. However, telehealth has been determined by other studies to be as effective as in-person care and provides a viable alternative for those who cannot go to in-person treatments[23], and in this particular study's cohort, the percentage of people using it increased from 9.7% to 63.7%. However, the lack of interpersonal interaction may have had some impact on PD patients suffering from the isolation of the pandemic.

		Never	Sometimes	Often	Almost Always
1	I felt I was close to panic	0	1	2	3
2	I found it difficult to work up the initiative to do things	0	1	2	3
3	I felt down hearted and blue	0	1	2	3
4	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
5	I felt that I had nothing to look forward to	0	1	2	3
6	I felt scared without any good reason	0	1	2	3
7	I tended to over react to situations	0	1	2	3
8	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
9	I found it difficult to relax	0	1	2	3
10	I couldn't seem to experience any positive feelings at all	0	1	2	3
11	I felt annoyed by people that criticised my drinking or drug use (if not applicable, mark "not at all")	0	1	2	3
12	I have thoughts of ending my life	0	1	2	3

Figure 3. Depression Anxiety Stress Scale(DASS-10), developed by Halford, 2021.

Covid-19 & Parkinson's Disease Symptoms

Although perhaps one of the largest concerns of PD patients during the pandemic, research focused on the relationship between SARS-CoV-2(severe acute respiratory syndrome coronavirus-2), COVID-19, and PD(increased susceptibility, mortality, worsening PD symptoms, etc) has provided conflicting results and is largely inconclusive[24]. Concerns about PD being an increased risk factor for COVID-19 have been researched by various studies. For now, data does not indicate that PD is a risk factor for developing Covid-19. A case-control study from Lombardy, Italy[25] aimed at concluding whether or not PD patients were at a greater risk of COVID-19 interviewed 1,486 PD patients and 1,207 family members. 7.1% of PD patients and 7.6% of family members were identified as COVID-19 patients, indicating that COVID-19 risk did not seem to differ from the general population. In addition, 5.7% of PD patients and 7.6% of those COVID-19 cases died from the disease, also indicating no increased risk in mortality rates either. However, in contrast, one study found that PD symptoms worsened in eight PD patients diagnosed with COVID-19 [26]. Infections have been found to increase the severity of Parkinson's symptoms and further motor deterioration may continue following a period of infection[24]. Unsurprisingly, the idea that Covid-19 respiratory infections can have detrimental effects on motor symptoms was entertained. As mentioned previously, the heightened stress and anxiety from a Covid-19 diagnosis in a PD patient alongside social isolation is also likely to exacerbate negative effects on motor and non-motor symptoms of PD.

Despite how the negative impacts of COVID-19 spread globally, it seems to have especially added significant layers of stress and anxiety for those with PD, further complicating an already difficult disease to navigate. Not to mention, the impact of the convergence of PD and COVID-19 is further compounded by socioeconomic factors, adding yet another additional layer of complexity.

Socioeconomic Factors of Parkinson's Disease

Socioeconomic factors ranging from income, employment, education, etc determine the choices readily available in a person's life, playing a huge role in disease and healthcare in particular. Lower socioeconomic status(SES) is generally associated with higher rates of disease, and as such there has been research focused on finding the association between socioeconomic status and prevalence of PD. After all, it is not unfounded to assume a connection, since it is unlikely that those of lower SES are unable to access proper healthcare, leading to a downward trajectory of increased morbidity and further increase in poverty and inaccessibility to care[27]. In a 2002 U.S. study, out of 50,000 participants, 27% of those who did not obtain proper medical care stated cost as the reason.[28] The inability to access proper care due to lower SES can also be credited to a multitude of subfactors as well, with a previously discussed study above finding that amongst 38 PD patients, the average years of education was around 6 years, while amongst 20 that did not have PD were found to have an average of 11 years in contrast[19]. Lower SES has also often been associated with the inability to receive proper education, and limited education leads to difficulty in finding an adequate job, therefore leading to increased poverty and inaccessibility to healthcare. And because this is a fairly new study conducted during the pandemic period, an assumption can be made that this harmful cycle is still ongoing today.

A 2009 study from Manitoba, Canada looked to explore the association between SES and prevalence and incidence of PD; also taking into account geographic location. Note the distinction between prevalence and incidence: prevalence is the measure of a population who have a specific characteristic in a given period, regardless of the time of occurrence, while incidence is a measure of the number of new cases of a characteristic that develops in a population in a specific period.[29] The Canadian healthcare system also operates differently from other countries, so the results of the present study may not be completely applicable to other locations.

Information for this study was collected using administrative data, hospital abstracts, physician billing claims, and health insurance registration forms. The total number of PD cases collected from physician billing claims increased from 43.4% at the beginning of the study to 76.4% during its last year, while the percentage of cases identified from hospital and physician data decreased from 52.1% to 19.4%. Over the entire study, it was also found that 3.8% of lower-income quintile cases and 4.2% of higher-income quintile cases were collected using specifically hospital data, while 36.8% of lower-income quintile cases and 36.0% of higher-income quintile cases were identified using both hospital and physician data. The study also revealed prevalence estimates from the first year ranging from 166.1 for the high-income rural income quintile to 201.1 for the lowest urban income quintile, and the last year ranging from 344.1 to 463.4 respectively. Note that analyses revealed that overall, the differences between lower-income urban and rural quintiles and higher-income urban and rural quintiles were not significant. In conclusion, the collected data found that prevalence rates were higher in lower income quintiles for both rural and urban areas than in the higher income quintiles and that incidence rates were higher in the lowest urban income quintile than in the highest urban income quintile. Prevalence of PD was also found to increase over time with the relative rate of increase being greater in the lowest income quintiles in comparison to the higher ones.

Although it is very difficult to identify specific reasons for these results, given the limited research connecting socioeconomic factors and PD, assumptions can be drawn given previously discussed factors. Perhaps these higher rates of PD in lower income quintiles can be attributed to previously discussed environmental exposures to heavy metals and contaminants since it is more likely for those from lower income areas to take on lower-level jobs such as construction laborers, manufacturing jobs, agricultural workers, etc that may have such exposures. Although the present study found no significant difference between urban and rural areas in low-income quintiles, a loose assumption can be made that low-income rural areas have greater exposure to environmental contaminants, such as previously discussed pesticides, and could theoretically have higher rates of PD. However, it is also important to take note that since these lower-income areas have less access to proper healthcare, it is possible that many may not have ever received a proper PD diagnosis and therefore were not included in the data presented in this study. A multitude of factors could play against each other to determine the connections between SES and PD, and therefore, nothing is truly definitive.

Figure 4. Social Factors of Parkinson's Disease

Treatment Options/Disease Management

Although Parkinson's Disease has grown to become the second-most common neurodegenerative disease with increasing numbers of cases in the U.S., there is currently no known cure for the disease. However, there are a multitude of widely accepted treatment options used to manage symptoms and maintain quality of life, as well as many other experimental treatment options. Many of these treatment options are targeted to protect dopaminergic neurons or to "rescue" neurons at risk.[30]

Common Pharmacologic Options

Levodopa, an amino acid, in combination with a peripheral decarboxylase inhibitor, is the most commonly prescribed treatment for PD. Levodopa is used to replace dopamine in the brain to reduce PD symptoms of slowness, stiffness, etc. The peripheral decarboxylase inhibitor frequently paired with the drug is meant to reduce peripheral side effects and enhance absorption[30], since blood enzymes tend to break down most of the levodopa before it can be converted into dopamine.[31] However, levodopa is not meant to completely stop the progression of the disease, and there have been some concerns regarding its long-term effects, as PD patients treated with the drug have seen developments of motor complications after 4-6 years.[32] One such complication that is attributed to levodopa therapy is dyskinesia, an overexpression of movement causing involuntary or erratic movements.[32] A 2004 study even evaluated the possibility of levodopa accelerating neurodegeneration instead. Theoretically, levodopa could enhance oxidative stress since levodopa and dopamine can generate reactive oxidative species and be toxic to cultured dopaminergic neurons.[33] The results of the study were contradicting, as data showed that levodopa seemed to slow the progression or had a prolonged effect on PD symptoms while neuroimaging data suggested that levodopa, instead, accelerated the loss of nigrostriatal dopamine nerve terminals. As information regarding PD usually is, levodopa's benefits short and long-term as a treatment option are still somewhat uncertain.

Dopamine agonists(DAs) are a group of medications that activate the dopaminergic receptor by mimicking the role of chemical messengers in the brain.[31] There are two different groups of DAs: ergoline(ex. hydergine) and non-ergoline derivatives(ex. pramipexole).[32] Only the non-ergoline derivatives are accepted as safe and recommended for treatment, as ergoline derivatives were found to cause severe side effects.[32] There is a wide range of DAs that can be prescribed alone or alongside levodopa and don't have a high likelihood of long-term complications in comparison to the drug.[32] However, DAs generally have more short-term side effects than levodopa does.[32]

Nonpharmacologic Treatments

Alongside various medications, exercise, speech therapy, and physical therapy interventions are also common nonpharmacologic treatments targeted at improving PD symptoms. A 2017 study aimed at finding long-term effects of exercise and physical therapy in PD patients found that most progressive strength and aerobic endurance training programs have positive effects that last for 12 weeks.[34] The study also cited that regular participation in these programs for periods alongside tai chi and dance therapy has been shown to improve muscle strength, walking capacity, and balance, resulting in decreases in fall risk. In particular, PD patients suffering from axial motor symptoms, symptoms that affect someone's axis, can benefit from these therapies. Common examples of these symptoms are freezing of gait(FoG), an episodic gait pattern where a person is unable to step[35], and camptocormia, a severe flexion of the trunk[32]**.** Most medications for PD are not targeted directly towards relieving axial motor symptoms, so physical therapy to combat these is especially effective and important.

Conclusion

PD continuously presents unique challenges to scientists and researchers today because of how little concrete information we know about it. Contradictions about the effect of heavy metals on PD onset are just one of many instances of PD research finding strong evidence supporting one theory and finding something contradictory in another. Additionally, study results may not apply to the entire PD population if they are done at different locations. Since, as explained above, outside factors like socioeconomic status and contact with certain environmental contaminants can have considerable effects on PD prevalence and onset depending on location. For example, the genetic studies mentioned above from Pennsylvania and Cambridge yielded entirely different results, and the most commonly found genetic variant in Japan was different from what had been recorded in America. In addition, even the most widely accepted treatment options for PD aren't long-term, and with the negative effects of the COVID-19 pandemic on the mental states of most PD patients, the need for more innovative therapies and treatments has become increasingly more important. And so, because of the limited knowledge we have relating to PD as a whole, the best thing we can do at the moment is to keep continuing research efforts, advocating for comprehensive care, and supporting those in the PD community to both enhance our understanding and improve the lives of those affected by this condition. Every breakthrough that is made in PD research, such as the conclusive study on MPTP's effects on inducing parkinsonism, is a major step in the right direction to finding long-term treatment.

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