Parkinson's Disease - Biomarkers, Current and GPR37

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ABSTRACT

Parkinson's disease, first diagnosed in 1817, is a progressive neurodegenerative disease widely known for its crippling motor symptoms, mainly tremors. The symptoms of Parkinson's have a large range and differ from patient to patient, but nonetheless, they are crippling. Biomarkers have been researched for Parkinson's for just as long, however, none have been truly reliable with high efficacy. For that reason, the search for biomarkers for Parkinson's still continues, even today, and with the recent discovery of the GPR37 receiver within the cerebrospinal fluid, there is a possibility for the search to end. The unique properties of the receiver make it especially promising, warranting an increased amount of research with regards to its efficacy and reliability in order.

Introduction

Imagine a normal morning, nothing out of the ordinary. You are eating breakfast, a bowl of the same cereal you have had for the past two weeks. Suddenly, you are struggling to pick up your fork. You attempt to bring the fork close to your mouth, but your hands shake and you spill milk all over the table. You are stuck, and you are unable to move your hand back down. Fatigue and pain suddenly shoot throughout your body and you drop the fork. All of these symptoms are experienced by someone with Parkinson's disease, the second most common neurodegenerative disease found in humans. Their normal lifestyles are completely ruined by their symptoms, and they have to find ways to adjust, since, as of today, there is no definitive cure for Parkinson's. There are many biomarkers that scientists use in order to diagnose PD, as Parkinson's disease has been actively researched since the early 1800s. Although this is true, there are no widely used biomarkers that have 100% efficacy, and for that reason, they are unreliable. When diagnosing Parkinson's disease, the symptoms appear way too late, and by then, there is no way to reverse the damage done to the nervous system. This proves the importance of finding certain biomarkers, characteristics of the body that are measurable and key in diagnosing Parkinson's disease early so that treatment is possible. As of right now, there are no completely reliable biomarkers that are effective in diagnosing Parkinson's disease, but the recent discovery of the GPR37 receiver found in the cerebrospinal fluid may be the needed neurochemical biomarker key in the diagnosis of Parkinson's disease.

Parkinson's Disease

Overview

Parkinson's disease is a neurodegenerative disease that starts in the substantia nigra, a part of the brain responsible for the production of dopamine, a key chemical needed for feelings of pleasure, along with learning,

retaining memory, motor function, and more. The level of dopamine is decreased in the brain as a result of dopaminergic cell death. The loss of dopamine results in motor deficiency, along with many non-motor symptoms. The motor features of Parkinson's disease can be grouped under the acronym TRAP. The acronym stands for *T*remor at rest, *R*igidity, *A*kinesia (also known as bradykinesia), and *P*ostural instability. However, Parkinson's disease affects people differently, and there is a wide range of possible symptoms, both movement-based and non-movement-based. Parkinson's disease is usually diagnosed at a late stage where full treatment is not possible due to the long latency between the first time dopaminergic cell death occurs and symptoms actually start to show up.
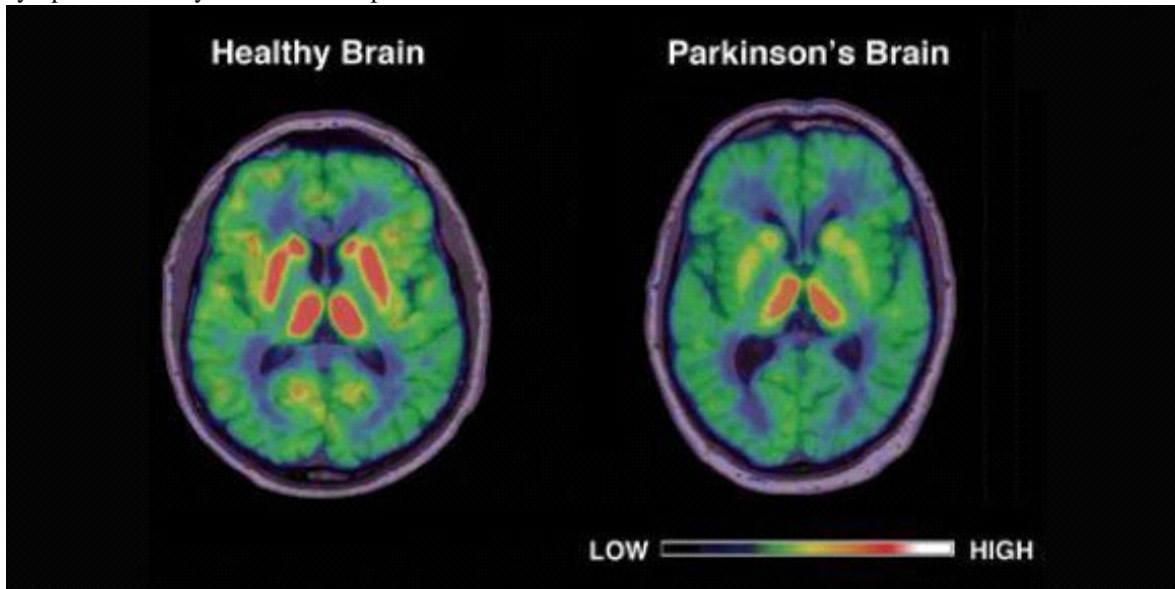

Figure 1. MRI scan displaying the brain of control and the brain of a patient that has developed Parkinson's disease (Sutherland 2021)

Motor Symptoms

Out of all of the possible motor symptoms that can be caused by Parkinson's disease, there are a few main ones that are characteristic symptoms of Parkinson's. These include Akinesia (typically known as bradykinesia), tremors, rigidity, postural deformities and instability, and freezing. Akinesia, or bradykinesia, is the most characteristic symptom of Parkinson's, and it is involved with movements being slowed down. Bradykinesia initially presents itself in the form of slowness in daily tasks and slower reaction time, but it can also include losing the ability to move and gesture spontaneously, increased drooling due to the impairment in the ability to swallow, monotonic and hypophonic dysarthria (speech impairment), decreased facial expression, and decreased amount of blinking. Although bradykinesia is the most characteristic symptom of Parkinson's disease, the most common and easily recognized symptom of PD is tremor. Most are hand tremors, but they can also be within the lips, chin, jaw, and legs. Additionally, some Parkinson's patients report that they feel an internal tremor, not externally visible. Rigidity is just an increased resistance when attempting to move a limb. Rigidity occurs proximally (eg. within the neck, shoulders, and hips), and distally (eg. within the wrists and ankles). Rigidity within the neck and the trunk has the possibility of resulting in abnormal postures (postural deformities). Skeletal abnormalities are also experienced by Parkinson's patients, such as extreme neck flexion, truncal flexion, and scoliosis as well. Postural reflexes are lost due to Parkinson's disease, and that leads to postural instability. It usually manifests itself in the later stages of Parkinson's disease, and it is the most common cause of falls and is significant in the risk of hip fractures. The loss of postural reflexes is not the only cause of postural instability, as orthostatic hypotension, age-related kinesthesia, and other parkinsonian symptoms all influence the occurrence of postural instability. The final motor symptom is freezing,

and it is the most disabling symptom of Parkinson's disease. It is a severe form of akinesia (bradykinesia), and it is also referred to as a motor block. Freezing usually affects the legs while walking, but it can also affect the arms and eyelids. There are five different types of freezing, start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation, and open space hesitation. However, these are only the motor symptoms associated with Parkinson's disease. There are also many non-motor-based symptoms associated with Parkinson's disease (Jankovic 2021).

Non-Motor Symptoms

Although Parkinson's disease has a sizeable amount of motor symptoms, there are a number of common and under-talked-about non-motor symptoms, including autonomic dysfunction, cognitive/neurobehavioral disorders, and sensory and sleep abnormalities. Autonomic failure, also known as autonomic dysfunction, features orthostatic hypotension, sweating dysfunction, erectile dysfunction, and sphincter dysfunction. Motor symptoms are extremely disabling, but neuropsychiatric disturbances (cognitive/neurobehavioral disorders) can be just as disabling. Patients diagnosed with Parkinson's disease are statistically six times more likely to be diagnosed with dementia in the future compared to healthy adults. Along with dementia, Parkinson's patients frequently reported depression, apathy, anxiety, and hallucinations. Additionally, Parkinson's patients reported obsessive-compulsive and impulsive behavior. This included sugar cravings, binge eating, pathological gambling, compulsive shopping, and sorting and arranging objects. Sleep disorders and abnormalities used to be attributed to the medication relating to Parkinson's disease, but some now believe that sleep abnormalities are linked to the disease itself. One symptom known as rapid eye movement sleep behavior disorder is characterized by violent dream content, which makes the person affected talk, yell, swear, grab, punch, kick, jump, and pursue other violent activities. Insomnia is highly variable among patients, but some patients are affected by this sleep disorder (Jankovic 2021).

Parkinson's Disease Symptoms	
Movement-Based	**Non-movement Based**
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioral and psychiatric problems
Decreased arm swing, shuffling gait, festination, difficulty arising from a chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea), weight loss
Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behavior disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

Figure 2. Table displaying the wide range of different motor and non-motor symptoms associated with Parkinson's (Jankovic 2021).

Biomarkers

Overview

Biomarkers are measurable values recorded in order to find quantitative and comparable data. Common bi-omarkers are simple things such as blood pressure and heart rate. The importance of biomarkers stems from the fact that these are types of quantitative data, and abnormalities from the normal values measured in healthy humans have the ability to diagnose diseases, such as Parkinson's disease. The biomarkers used in the diagnosis of Parkinson's are typically put into two categories. These categories are neurochemical biomarkers and neuroimaging biomarkers. As stated in the introduction, the currently used biomarkers in the diagnosis of Parkinson's are not as reliable as desired, and the detection of Parkinson's is at a stage where the complete treatment of the disease is impossible, as it is too late in its progression for modern-day medicine to fully cure (Emamzadeh and Surguchov 2021).

Currently Used: Neurochemical Biomarkers

As of right now, there are a few main neurochemical biomarkers used in the diagnosis of Parkinson's disease. The first of these is orexin, also known as hypocretin. It is a neuropeptide hormone that is expressed by a very small number of neurons of the dorsolateral hypothalamus in the brain. This hormone regulates the sleep-wake cycle, cardiovascular responses, heart rate, hypertension, and many other physiological body functions. The concentration of orexin within the body is inversely proportional to the severity of the disease. This means that the lower the concentration of orexin, the greater the severity of the disease. The second neuro-chemical biomarker for Parkinson's is 8-Hydroxy-20-Deoxyguanosine, which is the oxidized form of 8-hydroxyguanine. 8-OHdG is a biomarker of DNA damage and an increased concentration of 8-OHdG com-pared to a normal healthy adult concentration is an indicator of Parkinson's. However, it is not very reliable, as it is a marker of DNA damage, so it is possible that the reasoning for this is unrelated to Parkinson's dis-ease. The final biomarker is α-Synuclein, a newer biomarker that has received much recent attention due to its potential as a biomarker for Parkinson's. The form of α-syn found in humans is expressed within the neocor-tex, the hippocampus, the SN, the thalamus, and finally, the cerebellum. Levels of α-syn change in Parkin-son's patients, and evidence has shown that the α-syn can be secreted into the extracellular area within the brain, and a high concentration of α-syn within the extracellular fluid can damage healthy neurons and cause Parkinson's disease. Of course, many different neurochemical biomarkers for Parkinson's are not stated, but these are some of the main ones used (Emamzadeh and Surguchov 2021).

Currently Used: Neuroimaging Biomarkers

Using technology, it is possible to image the brain using different techniques in order to look for abnormali-ties unique to Parkinson's disease. The first technique used is transcranial B-mode sonography. This monitors the speed of blow flow within the brain. This method is inexpensive and reliable, and it shows higher levels of echogenicity within the SN for Parkinson's patients. This is due to the fact that there are increased levels of iron and gliosis levels found within the SN. This occurs because of either malfunction in the BBB (blood-brain barrier) or an alternation within the BBB. The second neuroimaging biomarker is magnetic resonance imaging, typically known as an MRI. Specifically, diffusion-weighted imaging is used in the detection of Parkinson's. A version of an MRI, it measures the rate of water diffusion through a certain tissue. This meth-od determines the structural details of that tissue. A higher measured diffusivity could be caused by cell death (Parkinson's disease). The two last neuroimaging biomarkers are SPECT scans and PET scans. SPECT stands for single-photon emission computed tomography, and it uses radiotracers and computer technology in order to generate 3D images. The radiotracers used are non-invasive and have a short lifespan. This is important because they are able to quickly decay after the scan is over. In SPECT scans, the radiotracers are made up of iodine and technetium that emits gamma rays, and they typically last longer than the radiotracers used for PET scans. This method has the ability to find reductions of DAT within the brain. Additionally, the amount of vesicular acetylcholine transporter (VAChT) can be monitored by the SPECT scan, which is important for

Parkinson's disease because ACh is supposed to be balanced with dopamine. When Parkinson's occurs, there is a higher amount of ACh compared to dopamine. PET stands for positron emission tomography, and these scans use anti-particles that have a similar mass to an electron. This method can also sense the presence of DAT in dopaminergic neurons. This can detect dopaminergic cell loss and damage, thus being able to detect Parkinson's disease (Emamzadeh and Surguchov 2021).

GPR37 Receiver

The GPR37 receiver, as stated previously, is found within the cerebrospinal fluid. This is good for experimentation and implementation due to the fact that cerebrospinal fluid is an accessible source of proteins developed in the brain. These proteins mirror molecular changes occurring in the central nervous system, making them good biomarkers. For example, amyloid-β and tau protein species are both found within the cerebrospinal fluid, and if the levels of these are lower than normal, it is usually a sign of Alzheimer's disease, the most common neurodegenerative disease found in humans. However, from past to current, all cerebrospinal fluid biomarkers used for Parkinson's have been widely inconclusive. The GPR37 receiver, however, is an "Orphan G protein-coupled receptor (GPCR) expressed in brain regions such as cerebellum, corpus callosum, caudate nucleus, putamen, hippocampus and SN." The experiment conducted by these researchers went on to test the difference in levels of GPR37 within the cerebrospinal fluid between Parkinson's patients, control patients, and Alzheimer's patients in order to find whether or not the difference in the levels of GPR37 were significant enough to consider it a working biomarker. Additionally, they tested levels of α-synuclein between the three patients to see if there would be a difference in the levels in order to prove reliability. The results of the experiment proved that "GPR37 protein density and mRNA expression were significantly augmented in sporadic PD... However, the CSF total α-synuclein level in PD patients did not differ from that in NC subjects. Similarly, the cortical GPR37 mRNA expression and CSF ecto-GPR37 levels in AD patients were also unaltered." This difference in levels proves the possibility that the ecto-GPR37 and GPR37 receivers are biomarkers for Parkinson's disease. What makes these biomarkers even more exceptional is the fact that their levels in patients with Alzheimer's disease are, more or less, stable. Alzheimer's disease and Parkinson's disease are extremely closely related, and for that reason, biomarkers for Parkinson's tend to detect Alzheimer's as well, leading to false alarms and inefficacy. Ecto-GPR37 and GPR37 do not have such issues with Alzheimer's disease, and for that reason, have high efficacy rates (Morató et. al. 2021).

Conclusion

Currently, there are no widely used biomarkers that are 100% reliable, available, and have the ability to diagnose Parkinson's early enough. Parkinson's patients' lifestyles are completely changed by their symptoms, and they are forced to find ways to adjust, since, as of today, there is no definitive cure for late-stage Parkinson's disease. Early detection becomes key here, proving the need for reliable and effective biomarkers. GPR37 was used in an experiment, trying to use it as a biomarker for Parkinson's, and the results were appalling. The levels of GPR37 within the cerebrospinal fluid were abnormally high in Parkinson's patients, but normal in both Alzheimer's patients and control patients. This biomarker seems to be increasingly promising, and more implementation of this biomarker may be the single key needed in order to defeat Parkinson's disease. However, of course, more studies must be pursued to further prove the efficacy of this biomarker and make sure there are no other implications with different diseases triggering false alarms, a common example being Alzheimer's disease. With the discovery of GPR37, the future for the development of Parkinson's disease detection and treatment looks bright.

Acknowledgments

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