Parkinson's disease: normal physiology and homeostasis

Introduction

Parkinson's disease, also known as paralysis agitans, is a common neurodegenerative disorder which generally manifests with motor abnormalities because of a loss of neurons in the substantia nigra whose nerve endings produce dopamine in the caudate nucleus and putamen in the brain. (7) It affects 2-3% of senior citizens and can include a combination of motor and non-motor symptoms which affect the peripheral nervous system, autonomic nervous system, brainstem, and cortex. Patients tend to experience non-motor defects before motor defects and have different rates of disease progression and symptom presentation, possibly because of a genetic component. (12)

Epidemiology

According to Williams-Gray, PD mostly affects 2-3% of those who are above 65 years of age but may occur at 30-40 years if a genetic component is present. (12) Globally, PD occurs in 1-2 out of 1000 people. Since genetics seems to play an important role in the disease, according to Tysnes and Storstein, at least one genetic factor of has been identified in 5-10% of the cases. Although not proven yet, it is hypothesized that environmental factors may also play a role in contributing to a higher risk in PD. (11) And 3-5% of these genetic cases are caused by a Mendelian fashion single genetic variant. (12)

Etiology

The causes of PD are unknown but are assumed to have a strong genetic component. (11) One important gene involved in PD is the glucocerebrosidase gene (GBA) in which a homozygous mutation causes Gaucher's disease and a heterozygous mutation may cause PD. Cases with a mutation in GBA have a faster disease progression and result in earlier cognitive decline. Other genetic mutations associated with PD include catechol-O-methyl-transferase (COMT) Val(158) polymorphism, microtubule-associated protein tau (MAPT), and apolipoprotein E (APOE). Other genes that may play a role in causing PD include SNCA, LRRK2, EIF4G1, and VPS35 which are autosomal dominant and Parkin, PINK1, and DJ1 which are autosomal recessive.(12)

Since dopamine is an inhibitory neurotransmitter, and a patient with PD has damaged dopaminergic neurons, this patient experiences symptoms of over activity because of continuous stimulation of excitatory signals and a lack of inhibitory signals, which may be the cause of the hallmark rigidity and involuntary tremor seen in PD patients. The akinesia, or difficulty in initiating voluntary movement seen in patients can be attributed to the decrease in dopamine release in the nucleus accumbens and basal ganglia, which requires the patient to concentrate exquisitely even on a simple task and does not result in a smooth, normal movement but instead in a stiff, harsh movement.(7) But according to a study done by Mirdamadi, it was proposed that PD has both cerebellar and basal ganglionic dysfunction and the level of sensory integration associated with the cerebellum, in patients with PD. (10)

Types/ Classification

All types and subtypes of PD can be collectively referred to as Parkinsonism. In a survey conducted by Bergareche and team, it was found that 1. 5% of the 2000 cohort sample, had PD while 1. 1% had other types of parkinsonism but that the presence of all types of Parkinson's increased with age and had no significance in relation to gender. (1) 80% of patients with Parkinsonism have idiopathic Parkinson's disease (IPD), simply referred to as PD. Other, more rare types of Parkinsonism include Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Dementia with Lewy Bodies (DLB), Vascular (arteriosclerotic) parkinsonism, and Corticobasal Degeneration (CBD). (9) After conducting punch biopsies in individuals with Parkinsonism, Wynford-Thomas and Robertson found that p-✓-synuclein can be found in dermal sympathetic nerve fibers of patients with IPD but not in patients with MSA, a method which can be used to further confirm a diagnosis of IPD. (13)

Normal Physiology and Homeostasis

The dopamine pathway is one of many neurotransmitter pathways that takes place in the basal ganglia, specifically from the substantia nigra to the caudate nucleus and putamen and transmits inhibitory signals along with the GABA and serotonin pathways. (7) Dopamine is heavily involved in motor control, arousal, and executive functions, which is why individuals with PD often have motor abnormalities. For an individual to function normally and carry out daily tasks, there has to be a balance between excitatory and inhibitory neurotransmission. Patients with PD lack dopaminergic neurons, therefore lacking dopamine, causing a disturbance of homeostasis and resulting in an excess of excitatory transmission. (2) Tyrosine is a precursor of dopamine and is converted to L-dopa by tyrosine hydroxylase. L-dopa is

then converted to dopamine by dopa decarboxylase but can also be converted into norepinephrine in the presence of β-hydroxylase. Normal dopaminergic neurons release dopamine because the presynaptic terminal contains tyrosine hydroxylase and dopa decarboxylase. Dopamine is degraded by COMT and monoamine oxidase (MAO). (4) MAO is found in presynaptic nerve terminals and oxidatively deaminates dopamine into 3, 4-dihydroxyphenylacetylaldehyde (DOPAL), which is then converted into 3, 4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase. Therefore, MAO inhibitors serve as a form of treatment for PD as they inhibit the activity of MAO, therefor inhibiting the conversion of dopamine to DOPAL, in order to sustain as much dopamine as possible in patients with PD. (8)

Pathophysiology and Molecular Basis of the Disease

PD occurs when there is a loss of dopaminergic cells in the substantia nigra of the basal ganglia in the midbrain. Aggregations of protein called Lewy bodies also occur in the presynaptic terminals. Specifically, Lewy bodies in PD are clusters of a protein called ✔-synuclein (coded by the SNCA gene) in the brain. (12) The SNCA gene was the first gene to be mapped, and is an important genetic factor in PD. (3) Lewy bodies start to develop in a predicted layout in the brain starting from the olfactory bulb and dorsal motor nucleus and spreading to the midbrain nuclei and forebrain, lastly reaching the temporal cortex. These aggregates of ✔-synuclein can spread across nerve synapses and therefore throughout the brain. The mechanism of initiation, how they spread, or in what rate they spread is still unknown and varies between patients. But one recent study by Del Tredici and Braak

suggests that initiation and proliferation of ✓-synuclein throughout the brain may be possible through an environmental trigger. (5)

Signs/ Symptoms

This disease can be classified by a combination of motor and non-motor symptoms. (12) The hallmarks of this disease include involuntary tremor, rigidity of musculature, akinesia, and bradykinesia. (7, 11) Non-motor features include but are not limited to depression, hallucinations, sleep problems, and cognitive disabilities. A common misconception has been that only motor abnormalities are important in the diagnosis of PD, but recent research has shown that even non-motor symptoms are now relevant to the disease's diagnosis, according to Williams-Gray. Since this disease may take many years to manifest and develop until symptoms are finally seen, some preliminary symptoms include loss of smell, constipation, mood changes, and REM abnormalities resulting in sleep disturbances. (12)

Laboratory Features

A diagnosis of PD is made by a neurologist based on medical history, family history, symptoms, and a review of systems along with a neurological and physical exam. The physical exam focuses on coordination, balance, muscle tone, and simple hand tasks. There is no specific blood test or scan that will give a concrete finding of PD and therefore it has to be diagnosed in a case by case basis. A comprehensive metabolic panel may be ordered to rule out liver damage or abnormal thyroid levels.(12)

Differential Diagnosis

Differential diagnoses for PD include but are not limited to: DLB, MSA, PSP, CBD, vascular parkinsonism, and Wilson's disease. Some non-neurological differential diagnoses of PD include arthritis, depression, obsessional slowness (OS), and psychogenic parkinsonism (PP). (6)

Complications and Prognosis

Since PD is a multisystem disorder and has many non-motor symptoms that occur before motor symptoms, taking note of the former symptoms may help with the diagnosis and the prognosis of the disease. Early recognition of clinical and genetic factors also helps with the prognosis and treatment of the disorder. Some of the current pharmacological treatments for PD include the following drug classes: levodopa (L-dopa), dopamine agonists, MAO-B inhibitors, COMT inhibitors, and anticholinergics. L-dopa therapy is most commonly used in early stages to control motor symptoms but has been found to be less effective overtime. (12) Although L-dopa helps with the rigidity and akinesia in PD, a complication is dyskinesia or uncontrolled involuntary muscle movement during use, a classic sign of a patient with PD. (7, 12) L-dopa is administered instead of dopamine because it is able to pass the blood-brain barrier and then is converted to dopamine, replenishing the lack which is found in PD patients. If dopamine was administered, it would not be able to cross the blood-brain barrier and would be futile in helping with PD. (7)

Complications may also arise with a dopamine agonist, which cause drowsiness during the day, ankle swelling, and a lack of impulse control, especially in patients with a family history of addictive behaviors. Out of all

the drug classes mentioned, L-dopa is preferred as it is better tolerated by most patients. But it is important to note that medication is prescribed on a case to case and severity basis. Dopamine agonists, COMT inhibitors, and MAO-B inhibitors may be used in combination with L-dopa to treat motor symptoms and slow dopamine metabolism, therefore decreasing motor abnormalities. (12) Invasively, treatment by destruction of parts of circuitry in the basal ganglia or the use of deep brain stimulation is also an option for patients with less neurological problems. But surgical intervention has had variable results in different patients, and is not considered the first course of action in PD. (7)

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