What is Parkinson's Disease

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Parkinson's disease (PD) is a progressive disorder of the nervous system. With an annual incidence of approximately 20 new cases per 100,000 people, the prevalence is 200 cases per 100,000 people or 0.2%. There are 1,000,000 or more people with PD in the United States; more patients than with multiple sclerosis, amyotrophic lateral sclerosis, muscular dystrophy and myasthenia gravis combined.

PD is generally age-specific; it is estimated that approximately 1% of the population over age 60 has PD. The occurrence of PD around age 60 suggests the disease may be time-locked to certain age-related changes in the nervous system. However, PD does occur in young people. Approximately 10% of all patients develop symptoms before age 50. This suggests that in addition to any changes related to aging, there are specific changes related to the disease.

PD is characterized by four main features: rigidity or stiffness of the arms, legs or neck; tremor, usually of the hands; bradykinesia or slowness and reduction of movement; and postural instability (loss of balance). Other symptoms may accompany the main features, including depression, dementia or confusion, postural deformity, speech and swallowing difficulty, drooling, dizziness on standing, impotence, urinary frequency and constipation.

When rigidity, tremor, slowness of movement and loss of balance dominate, when the course of the disease is slow with disability occurring 10 to 20 years after diagnosis, and when there is no obvious cause, then the condition is referred to as idiopathic PD. Patients with the above features, on post-mortem examination, show loss of the dark, pigmented neurons (nerve cells) in two areas of the brain: the substantia nigra (Latin for "black substance") and the locus ceruleus ("blue substance"). The dead and dying cells contain Lewy bodies. While Lewy bodies are found in other diseases, the diagnosis of idiopathic PD can only be made with certainty if Lewy bodies are found in the substantia nigra and locus ceruleus after death.

Paralleling the loss of nerve cells in the substantia nigra is the loss of dopamine, a chemical which carries messages from one nerve cell to another. The loss of dopamine is most marked in that part of the brain called the striatum (or "stripped substance"). The striatum consists of two parts: The caudate nucleus and the putamen. Primary treatment of PD consists of giving levodopa (in the U.S. via Sinemet or a generic form thereof), which is converted to dopamine in the substantia nigra and the striatum, and replaces the missing dopamine. Patients with idiopathic PD usually respond well to levodopa. In fact, a successful response to levodopa confirms the clinical diagnosis of PD.

When early in the disease there is a mixture of the main features with other symptoms; when the course of the disease is rapid with marked disability occurring within five years; or when there is no response to levodopa, the condition is called Parkinson Disease Plus (PD+). The term "PD+") encompasses a number of disorders including Progressive Supranuclear Palsy (PSP), Cortico-Basilar Degeneration (CBD) and MultiSystem Atrophy (MSA). MultiSystem Atrophy includes the Shy-Drager Syndrome (SDS), Striatonigral Degeneration (SND) and OlivopontoCerebellar Atrophy (OPCA). The PD+ disorders differ from idiopathic PD in that, although there is a loss of nerve cells in the substantia nigra and the striatum, and replaces the missing dopamine. Patients with idiopathic PD usually respond well to levodopa. In fact, a successful response to levodopa confirms the clinical diagnosis of PD.

There are also a number of disorders with parkinsonian features for which the cause is known and which have a variable rate of progression and response to levodopa. These disorders are referred to as Parkinson Syndrome (PS) and include multiple small strokes and poisoning by manganese, carbon monoxide and cyanide. PS also includes pugilistic parkinsonism, a disorder of professional boxers who receive multiple blows to the head and in whom symptoms progress even after they stop fighting. Pugilistic parkinsonism affected Jack Dempsey, Joe Lewis and, more recently, Muhammad Ali.

In addition to the above disorders, which are permanent, there are several drug induced Parkinson disorders that are reversible on stopping the drug. Drugs that cause PS include tranquilizers such as chlorpromazine (Thorazine), fluphen-zine (Prolixin) and haloperidol (Haldol). In addition, drugs such as metochlopramide (Reglan) and prochlorperazine (Compazine), used to treat nausea but similar to the tranquilizers, may also cause PS. These drug-induced disorders are not associated with a loss of nerve cells in the substantia nigra and differ from the permanent PS associated with the nerve toxin MPTP which does result in loss of nerve cells in the substantia nigra.
Diagnosis

The diagnosis of PD is based on finding a combination of rigidity, tremor, slowness of movement and lack of balance. The patient is often brought to the physician by the spouse and may not even be aware of any symptoms. The patient's lack of awareness may represent denial or a real inability to perceive the physical symptoms or depression. Computed tomography (CT) or magnetic imaging (MRI) are useful in excluding other causes of symptoms such as tumors or multiple small strokes. MRI is especially useful in excluding shrinkage of the brainstem and cerebellum, conditions that may be associated with some of the PD+ disorders.

Primary Features

While seldom the main symptom, rigidity is one of the four primary symptoms and is experienced as a stiffness of the limbs. In PD, rigidity is greater in the limbs whereas in PD+, rigidity is greater in the neck and trunk.

Tremor, at rest, is usually the earliest and most prominent symptom of PD, and is present in approximately 70% of patients. It is usually the symptom that brings the patient to the doctor. Patients with tremor usually have a longer and more "benign" course than patients without tremor. The tremor, initially, can involve one side more than the other and the hands more than the feet. The tremor is usually present when the limbs are resting; when the patient is seated with his/her hand supported or when the patient is walking with hands hanging loosely. The tremor usually stops when the muscles are activated. For some patients, the tremor may be more prominent when maintaining a posture (postural tremor). Occasionally the tremor may increase during movement (kinetic tremor) or the tremor may be prominent during writing (writing tremor). Postural or kinetic tremor are more common in Essential Tremor (ET) than in PD. Several types of tremor can coexist in PD including resting, postural, kinetic and writing tremor.

Bradykinesia is the most disabling symptom of PD. Bradykinesia includes slowness and loss of movement, delays in starting to move, frequent stoppages of movement, fatigue and inability to perform two movements at once, e.g. swinging the arms while walking. The PD patient who is bradykinetic differs from the patient who is weak or paralyzed. Weakness or paralysis is an inability to move because of a lack of power. The PD patient has enough power to move, but cannot move rapidly.

Postural instability results from impairment of the balance reflexes that are responsible for correcting equilibrium in response to positional changes. In PD, as a result of postural instability, patients fall easily. Postural instability may be experienced when a patient attempts to turn or enter a doorway.

The disturbance in walking in PD is characterized by short steps and results from a combination of rigidity, bradykinesia and postural instability.

Click here for Symptoms of Parkinson's.

Secondary Features

Secondary features may not be disabling and occur in less than 50% of patients. However, secondary features like speech and swallowing difficulty can become disabling.

Dementia, characterized by disorientation, confusion and memory loss, occurs in approximately 30% of patients with PD. Its prevalence increases with age and may be related to Alzheimer Disease (AD). The dementia of PD may be aggravated by treatment with levodopa and other drugs, especially anticholinergic and amantadine. The psychiatric side effects of antiparkinson drugs include an excited, confusional state with delusions or hallucinations.

Depression is frequent in PD, occurring in 50 to 75% of all patients. In 50% of these patients, the depression is severe enough to require psychological consultation or treatment with antidepressant drugs. Depression, in PD, may be either a reaction to having a chronic illness or it may be caused by a chemical imbalance. Supporting the idea that depression is a chemical imbalance are observations that depression may precede the other symptoms and that there may be no relationship between the severity of the depression and the severity of PD.

Facial masking results from a combination of bradykinesia and rigidity of the facial muscles. Disappearance of facial masking may be the earliest sign of successful treatment.

Speech difficulty may include a decrease in volume, a tendency for words to run together and slurring. The speech difficulty may vary from slight to marked. Some degree of swallowing difficulty is present in
many patients, but severe swallowing difficulty is uncommon, though it may occur in late PD. Speech and swallowing difficulties result from a combination of rigidity and bradykinesia in the muscles of the throat and mouth.

Other secondary symptoms include:

- Drooling and oily skin are common symptoms but are not disabling.
- Dizziness, in PD, is related to a drop in blood pressure on standing and may be aggravated by levodopa and dopamine agonists.
- Shortness of breath results from a combination of chest wall rigidity and abnormal, drug-induced muscle movement.
- Urinary problems occur in PD, usually taking the form of urgency. In elderly men, such urgency is more likely to result from an enlarged prostate.
- Constipation, a common symptom in the elderly, is frequent in PD and may be worsened by drugs, especially anticholinergic and amantadine.
- Impotence, another common symptom of the elderly, is also frequent in PD.
- Symptoms of burning or cold sensations, muscle cramps and joint pains also occur in PD.

The gold standard for confirming the diagnosis of idiopathic PD is finding Lewy bodies in the nerve cells of the substantia nigra after death. Approximately 75% of patients who are diagnosed with PD are found, after death, to have Lewy bodies. The inverse of the above is that 25% of patients who are diagnosed as having typical PD are found, after death, not to have Lewy bodies. This means that although Lewy bodies are, at present, the best markers for PD, their presence (or absence) is still not conclusive.

At least 60% of the nerve cells in the substantia nigra and 80% of the dopamine in the striatum must be lost before the first symptoms of PD appear. This indicates that the process of PD, as distinct from the recognized disease, is on-going for many years before it is diagnosed. The idea that there are a large number of seemingly "normal" people who have PD and who may, if they live long enough, develop PD symptoms, challenges physicians to develop methods for identifying these people so that treatment to slow progression, with drugs such as selegiline (Eldepryl), can start before PD becomes obvious.

Click here for secondary symptoms.

Cause

Research on the cause of PD centers on why the nerve cells in the substantia nigra and locus ceruleus die early while nerve cells in other areas are not affected. The presence of pigment (neuromelanin) in these nerve cells may provide clues since the pigment in these cells is derived from dopamine. An unrecognized environmental toxin (similar to MPTP) or a genetic defect may accelerate the loss of pigment. As nerve cells die throughout the course of PD, identifying the cause and halting the progress is a research priority.

Given how common PD is and how easily it can be recognized, it is surprising that the first description of PD was in 1817. This suggests that it may be related to an environmental toxin, a product of the industrial revolution. If environmental toxins are responsible for PD there should be variations in the occurrence of PD in different areas of the world. The occurrence of PD is similar in most Western countries, but less in the Mediterranean countries, Japan and China. Although there are no geographical clusters that would unequivocally establish an environmental cause, there is enough supportive data to encourage the continuation of environmental studies.

One observation linking environmental toxins to PD is a lower incidence of cigarette smokers among PD patients. This suggests there may be a substance in cigarette smoke that protects against an environmental toxin. Another observation linking environmental toxins to PD is the higher occurrence of PD in rural areas, where more herbicides and pesticides are used than in urban areas.

If PD is inherited, such a tendency might be revealed in studies of twins. In a study of 43 pairs of identical twins and 19 pairs of non-identical twins, in which one of the twins had PD, it was found that in only one identical twin pair did both twins have PD. Thus, the frequency of PD in identical twins was similar to what would be expected by chance alone. Other studies also failed to reveal an increased occurrence of PD in families. For a long time, then, it was believed that whatever the role of genetics was, it was subtle. Recently, appreciating that there may be a long delay in the appearance of the symptoms of PD, and using techniques such as positron emission tomography (PET) to detect PD before it can be recognized by a physician, the assumption that PD is not inherited is being questioned. While the exact role of genetics is unknown, it is more important than previously suspected.
The major finding linking PD to environmental toxins is the identification of the chemical MPTP as a cause of a permanent disorder similar to PD. The role of MPTP surfaced in 1977, when parkinsonism developed in a young man. Although no cause for the disease could be found, drugs were suspected. The patient committed suicide and his autopsy revealed loss of nerve cells in the substantia nigra. Subsequently, Dr. William Langston identified several patients with parkinsonism who had also been using drugs that contained MPTP. This observation, and subsequent observations by Langston and Burns that MPTP caused parkinsonism in monkeys, revolutionized thinking about PD. Whether MPTP or similar compounds play a role in causing PD is not known. The study of MPTP, however, has led to new insights into PD and in formulating strategies for halting its progress.

The virus that caused encephalitis (sleeping sickness) also caused symptoms resembling PD. This disorder is described in the book and movie by Oliver Sacks: "Awakenings." The parkinsonian symptoms caused by the virus appeared, in some, during the actual epidemic (1919 to 1926) while for others, symptoms appeared several years later: Post encephalitic parkinsonism. The viral disease progressed more slowly than PD. In the substantia nigra, there was greater loss of nerve cells, but without Lewy bodies. Although other viruses can, though rarely, cause parkinsonism, many studies have failed to reveal a virus as the cause of idiopathic PD.

Professional boxers who receive multiple, severe blows to the brain may develop a Parkinson Syndrome that is progressive. Severe head injuries with prolonged coma can result in a variety of movement disorders including Parkinson's Syndrome.

The mean age of onset of PD is 60 years. Thus, though not applicable to young-onset patients, age-related changes may be important in looking for the cause of PD, including:

- Age-related losses of nerve cells and pigment in the substantia nigra that peak at age 60. Since the pigment may protect the dopamine containing nerve cells from the effects of MPTP, toxins or free radicals, the loss of pigment may predispose the brain of older people to PD.
- Age-related loss of dopamine in the striatum. Although the distribution of the age-related dopamine loss in the striatum is different from the loss in PD, the age-related dopamine loss, coupled with the disease-related dopamine loss, may make the older brain more vulnerable to PD.
- Age-related increase in the amount of the enzyme MAO-B. The increase in brain MAO-B may promote the formation of toxic free radicals.
- Age-related increase of brain iron and an even greater increase of iron in PD. Brain iron is undetectable at birth, gradually increasing through the first three decades and concentrating in the substantia nigra and globus pallidus. Brain iron remains stable until the sixth or seventh decade when there is a further increase, particularly in the striatum. Iron is absorbed through the gut and transported into the brain by a protein called transferrin. Iron is stored within the support cells (glia), where it is bound to another protein, ferritin.

When iron is bound to protein it is harmless. When iron is not bound it is reactive and promotes the formation of free radicals. Several reports indicate that the increased iron in PD is free. Although there is evidence that the increased iron has a role in PD it is possible that the increased iron in PD is a secondary phenomenon.

**Disorders Similar to PD**

There are several disorders which, at one time or another in their course, may be mistaken for PD. These disorders may begin differently from PD, progress more rapidly and respond poorly or not at all to levodopa. Tremor at rest is usually not part of these disorders. Some of these disorders, especially the PD+ disorders, may be distinguished from PD by the presence of increased iron in the striatum on MRI. While it is probable that these disorders will be shown to have causes different from PD, it is conceivable that, ultimately, they may be shown to have the same cause.

**Progressive Supranuclear Palsy (PSP)**

PSP begins at about the same time as PD. It is one of the more common PD+ syndromes, with an occurrence approximately 1% of PD. PSP progresses more rapidly than PD with disability occurring after 3 to 10 years. PSP begins with falls, eye movement abnormalities and slurred speech. Tremor is usually absent. Click [here](#) for more information.
Multisystem Atrophy (MSA)

There are several disorders which, when well developed, are easily distinguishable from PD. These disorders are called Multisystem Atrophy (MSA) because, unlike in PD, more than one system degenerates. The Shy-Drager Syndrome, Striato-Nigral Degeneration and OlivoPontoCerebellar Atrophy are often grouped under Multisystem Atrophy.

Shy-Drager Syndrome

The main feature of the Shy-Drager Syndrome is dizziness on standing, with an occasional patient actually blacking out. This results from a drop in blood pressure on standing and reflects a loss of tone of the blood vessels that regulate blood pressure. Many patients with PD experience dizziness on standing, but it is not as severe as in the Shy-Drager Syndrome. The Shy-Drager Syndrome is much less common than PD. It appears at approximately the same age but progresses more rapidly.

Striatonigral Degeneration (SND)

SND is the disorder most commonly mistaken for PD. SND is characterized by rigidity, bradykinesia and impaired balance, but there is rarely a tremor. Patients will respond poorly to levodopa.

OlivoPontoCerebellar Atrophy (OPCA)

OPCA identifies a group of disorders whose common factor is a loss of nerve cells in the brainstem and cerebellum. There are inherited and non-inherited OPCAS. Disease onset ranges from under 1 year in familial OPCA to 70 years in non-familial OPCA. The course is very slow for familial OPCA, but more rapid for non-familial OPCA.

Essential Tremor (ET)

ET is usually a disorder of the elderly but it may begin at any age. It is slowly progressive and can usually be distinguished from PD fairly easily. ET may involve the head, voice and hands, but usually spares the legs. It is usually equal on both sides of the body and disappears when the limbs are relaxed, the opposite of the tremor in PD. ET may increase during specific activities such as writing, drinking and eating. ET is inherited in 30 to 50% of patients.

The relationship of ET to PD is unclear. Some PD patients, initially, may be diagnosed with ET. Within 2 to 5 years other PD features usually appear.

Click here for more information on Tremor.

Dystonia

Dystonia refers to either a sustained repetitive movement, that may be slow or rapid, or a sustained posture. Dystonia may occur as a separate disease entity in which it can be generalized, segmental or focal, or it may occur as a symptom of another disease such as PD.

Focal dystonia affects a single body part and includes blepharospasm (eyelid muscle spasm) and cramping of the hands or feet. Foot cramping may, in young people, occur as the first symptom of PD or may occur during levodopa treatment. The intensity of dystonia can be influenced by activities such as walking, running, talking or changing position.

Drug Induced Movement Disorders

Some drugs are especially likely to cause movement disorders. These include drugs that affect the dopamine system, including stimulants such as amphetamine, methylphenidate (Ritalin) and cocaine; drugs that mimic levodopa such as bromocriptine and pergolide; and dopamine blockers, or neuro-leptics, such as phenothiazines: Thorazine, Stellazine and Compazine. Also likely to cause movement disorders are the butyrophenones: Haldol and the antinausea drug metoclopramide (Reglan).

Stimulant drugs and levodopa can cause dyskinesias. Levodopa related dyskinesias parallel the severity of the underlying PD and the amount and duration of levodopa treatment. Dyskinesias are less likely to occur with dopa-mine agonists.

Tremor may be caused or aggravated by many drugs including steroids, anti-asthma drugs, caffeine, lithium, nicotine, thyroid hormones, certain anti-depressant drugs and anticonvulsant drugs such as valproic acid (Depakoate). Alcohol may both lessen and aggravate tremors.