PARKINSON'S DISEASE

The Disorder and Current Therapy

Parkinson's disease is a common neurologic disorder. It affects people of all ages and ethnic backgrounds and is seen in countries around the world. Parkinson's disease most begins between ages 55-60, although the majority of patients are over 65. Early onset Parkinson's disease is now more widely recognized. Approximately ten percent of Parkinson patients are under the age of 50 (juvenile onset.) It is estimated that 1 million Americans are affected, with 50,000 new cases diagnosed annually. It affects men slightly more frequently than women. Modern therapy has provided excellent treatment and control of many of the symptoms of Parkinson's disease but it still remains a progressive neurodegenerative disorder.

Historical Background

Parkinson's disease has been referred to in history as far back as the ancient Egyptians. Hieroglyphic writings make reference to the symptoms of the disease. The references to Parkinson's disease throughout historical literature include the Bible, writings of Galen-the-Great, a Greek physician of the second century and in Shakespeare's works.

In 1817 a British surgeon, James Parkinson, wrote an essay on *The Shaking Palsy.* In this paper he described the primary clinical symptoms of six patients affected with the disease. In the later 1800's, this clinical syndrome of tremor, rigidity and slowness of movements (bradykinesia) came to bear Dr. Parkinson's name.

Cause

The underlying disease process for Parkinson's disease was discovered in the 1950's. It was found that a specific area of the brain known as the *substantia nigra* *(http://www.med.uiuc.edu/m1/neurosci/Web_Neuro/movies/moviesOld/subthalsubnigra.mov)* was affected. The substantia nigra is a dark pigmented area located in the brainstem *(http://www.med.uiuc.edu/m1/neurosci/Web_Neuro/movies/moviesOld/subnigra.mov)*. It contains specialized nerve cells (neurons) that produce a neurotransmitter, *dopamine*. Dopamine is responsible for enabling the brain to generate signals for smooth, well-regulated motor (muscle) function. In patients with Parkinson's disease, the dopamine producing neurons slowly die off. This results in a dopamine shortage in the brain. Patients who develop symptoms of Parkinson's disease have already lost 80 percent of the dopamine producing

neurons. Despite extensive clinical research, the cause for the loss of these dopamine-containing neurons in the substantia nigra remains a medical mystery.

Clinical Signs & Symptoms

The primary clinical features of Parkinson's disease include rigidity, bradykinesia (slowness of movement), postural instability (loss of balance) and tremor. Tremor can begin insidiously as a slight shaking in one hand. It can then spread to involve the arm and usually spreads to the opposite side. This may occur over months to years. The characteristic appearance of the tremor is that of a *pill-rolling* motion between the thumb, index and middle fingers. Parkinsonian tremor occurs at rest and stops with movement of the hand or arm. This is a different type of tremor from the usual essential (*intention*) tremor. Essential tremor is characteristically more prominent when affected individuals are doing activities with their hands. Interestingly, shoulder pain can occasionally be the first presenting symptom of early Parkinson's disease. It is important to note that not all Parkinson patients have tremor. The reverse is also true: Not everything that shakes is Parkinson's disease.

Parkinson patients frequently complain of feeling stiff and weak. This is the characteristic of ***rigidity***. Muscles develop a plastic-like stiffness. Some patients may be more aware of this than others. They have difficulty getting out of bed, rolling over in bed or standing from a sitting position. Rigidity accompanies ***bradykinesia***, which is another hallmark of Parkinson's disease. Patients typically notice a slowing down of all their movements. There is a significant delay in their ability to complete routine tasks such as dressing, eating, standing and walking. It is the combination of bradykinesia and rigidity that make Parkinson's disease functionally disabling.

Postural instability, a problem with balance, can be a significant clinical problem. Associated with this is the characteristic stooped posture of Parkinsonism. Patients routinely complain of feeling off balance or unsteady. Some patients suffer from frequent stumbling and falls. This is due to the patient's inability to make the normal reflex adjustments to sudden changes in position that naturally occur when turning or walking. Patients may have difficulty with initiating walking or while walking, suddenly stop when going through a doorway. This is known as *freezing*. Once they start walking, they may assume a stooped posture and take a series of rapid, short shuffling steps as if they were running forward to keep themselves from falling. This is the typical Parkinsonian gait known as *festination*. Another balance problem that can affect Parkinson patients is the tendency to fall backward known as *retropulsion*. This is one of the most difficulty Parkinson symptoms to treat as there is no effective therapy, walker or exercise to prevent it.

Other common features of Parkinson's disease include a masked facial appearance. Patients lose the normal expressions of facial movement while at rest or when speaking. Their blink rate also diminishes and it may appear that

they are staring. The voice is also affected and speech may become slowed, very soft, and at times hoarse. Patients may speak in a monotone due to loss of normal speech inflection. The facial skin can develop a form of seborrhea that leads to an oily, scaly appearance. Daytime drooling is another common problem. It is not due to the overproduction of saliva but rather impairment of the swallowing reflex that normally clears saliva from the mouth as it is produced. Swallowing disorders are more commonly seen in the later stages of Parkinson's disease. Choking while eating may become a major problem and patients should exercise care to eat smaller bites and chew their food thoroughly. A Parkinson patient's writing typically deteriorates. Writing becomes progressively smaller (*micrographia*) and illegible.

The autonomic nervous system (ANS) is the part of our nervous system that regulates automatic functions of the body. These include blood pressure, stomach and intestinal function, sleeping, sweating, as well as some aspects of breathing, and urination. The ANS regulates body functions that we are normally not consciously aware of. A common problem among Parkinson patients is a sudden drop in blood pressure when they stand up. This can result in severe dizziness and even loss of consciousness. This condition is known as orthostatic hypotension. Constipation is seen in the majority of Parkinson patients. The normal intestinal motility slows down, much like the Parkinson patient's other movements. This can lead to chronic, persistent constipation. If left untreated it may lead to pathologic constipation (obstipation) and even bowel obstruction. The latter is a medical emergency and may be fatal if left untreated. For this reason, Parkinson patients should drink plenty of fluids and have a high bulk fiber diet.

Sleep abnormalities are not uncommon. Parkinson patients frequently have difficulty sleeping at night. This may be due to problems with daytime drowsiness and frequent naps. These naps should be avoided as much as possible. Sleep disorders may be associated with, or due to, breathing irregularities such as apnea, a recurrent temporary halting of normal breathing. Other breathing problems may occur such as rapid breathing or a feeling of shortness of breath. The latter is due to rigidity of the respiratory muscles in between the ribs. This problem is typically worse at night. Decreased visual function can also occur. Patients will frequently say that their eye exams are normal and yet they have trouble focusing. This is due to the decrease in dopamine in the retinal cells in the eye. Dopamine is an important chemical involved in good visual functioning. Urinary difficulties are common. Patients may have trouble starting urination due to difficulty in relaxing the bladder sphincter muscles. The opposite problem, urinary frequency, can also occur. Patients have a feeling of needing to void frequently but only produce a small amount of urine. This can lead to incontinence.

Psychiatric symptoms: Nocturnal hallucinations, agitation, and wandering at night can be a significant patient management problem. Not only

are these due to the disease process itself but can also be caused by the medications used to treat Parkinson's disease. Hallucinations are common. They are not always disturbing to the patient but may be frightening at times. Frequently they are caused by medications but can be related to the disease process itself. Sudden onset of paranoia or unwarranted suspiciousness can occur. Frequently this suspiciousness is directed toward the patient's spouse. If severe enough, patients sometimes have to be admitted to the hospital to prevent injuries to themselves and others.

Dementia (memory loss) is a significant and far too common problem in patients with Parkinson's disease. It is estimated that approximately fifty percent of all Parkinson patients will ultimately develop some degree of Parkinson associated dementia. This process starts slowly with mild degrees of memory loss. As it worsens forgetfulness, asking the same questions repeatedly and bizarre behavior become all too noticeable. Patients affected with this typically have a worsening of their symptoms at night (*sundowning phenomenon*), frequently becoming psychotic or more agitated. They may get dressed some time after midnight claiming that they are going to work, on vacation, to someone's house (typically the person is deceased) or to the theater. A patient may wander about, lost in his own house or neighborhood. When patients deteriorate to this point, serious consideration must be given to putting the patient in a more supervised living environment. The earlier treatment is started for Parkinson dementia, the better the long term prognosis is for these patients.

Depression occurs in many patients with Parkinson's disease. This can range anywhere from mild depression to a severe, disabling major depression. It is important for family members, caregivers, and medical personnel to be aware of this serious problem. Symptoms include loss of interest in activities or socializing, excessive fatigue, poor sleep patterns and irritability. Early identification and treatment of depression can significantly improve the patient's quality of life. Current therapies can provide rapid, excellent relief of this troubling problem.

Diagnosis

The clinical diagnosis of Parkinson's disease is based on patient symptoms and findings on neurological examination. There are no specific CT/MRI brain scan abnormalities or blood tests that confirm the diagnosis of Parkinson's disease. A physician may order certain tests to exclude other problems but the diagnosis of Parkinson's disease is based on detailed clinical history and physical exam.

There are several neurologic diseases that mimic Parkinson's disease. These syndromes have some of the clinical features of Parkinson's disease. They are not however, due to the dying off of nerve cells in the substantia nigra or due to dopamine deficiency. These syndromes are classified as atypical Parkinson's disease or Parkinson Plus syndromes. Common among these syndromes are progressive supranuclear palsy, Wilson's disease and cortical basal ganglionic degeneration (CBGD.) Patients affected with one of these diseases frequently do

not respond to the medications used to treat Parkinson's disease. All of these neurological syndromes, including Parkinson's disease, are in the family of neurodegenerative disorders. They are inexorably progressive usually over a period of five to twenty years.

Treatment

The symptoms of Parkinson's disease are due to a brain deficiency of the neurotransmitter dopamine. The most logical approach to correcting this problem is to replace the dopamine (DA). Unfortunately one cannot take dopamine orally as it does not cross the blood brain barrier (BBB). A chemical precursor to DA, levodopa (L-dopa) can cross the BBB. L-dopa is then converted in the brain to dopamine. L-dopa was introduced for treatment of Parkinson's disease in the late 1960's. L-dopa therapy is the gold standard treatment for Parkinson's disease. As a general rule, unless a patient has an exuberant response to L-dopa therapy he/she most likely has an atypical Parkinson syndrome.

L-dopa is a naturally occurring substance. It is in the chemical family of compounds known as amino acids. Amino acids are the building blocks of proteins. L-dopa can be taken orally. Its absorption can be reduced if taken with a high protein meal. Once absorbed, L-dopa is converted to DA in the blood, liver and kidneys. Some of it crosses the BBB into the brain where it is then converted to DA. Only the L-dopa that crosses the BBB has any beneficial clinical effect. A compound called carbidopa is given with L-dopa. Carbidopa inhibits the enzyme in the liver, kidneys, and blood that converts L-dopa to DA. This allows more L-dopa to pass into the brain. It also minimizes some of the side effects of L-dopa therapy. Carbidopa does not cross the BBB. Sinemet CR is a longer acting, controlled release form of carbidopa/L-dopa. Sinemet, Parcopa and Stalevo all are "regular" carbidopa/levodopa preparations.

Once a patient's activity of daily living becomes compromised by the Parkinson symptoms, L-dopa therapy almost always improves the patient's quality of life. The patient's speech, gait, functional abilities and general movements are much better. L-dopa therapy is very effective in relieving the symptoms of Parkinson's disease, particularly the symptom of rigidity. Tremor can be significantly reduced by L-dopa therapy although responses may vary from patient to patient. Early in the course of Parkinson's disease, bradykinesia responds favorably to L-dopa. Here again patients may have a variable response to therapy. In later stages of Parkinson's disease, bradykinesia can be a significant problem as it becomes less responsive to L-dopa. It is preferable to delay starting L-dopa therapy in early Parkinson's disease. There are several other different medications that are effective in treating early symptoms.

L-dopa therapy can maintain this functional improvement for several years. Unfortunately this effect eventually wears off. This can be anywhere from four to ten years or more. In general, L-dopa has a useful clinical window of five to seven years. After this patients can have significant side effects including

dyskinesias and other ***motor fluctuations***. Dyskinesias are uncontrolled involuntary head, trunk, arm and leg movements. Patients may have writhing movements of their head and extremities. They frequently have tricks to suppress some of this activity, such as sitting on their hands or crossing their arms. Development of dyskinesias is related to the duration of L-dopa therapy and the total daily dosage amount. The longer a patient is on L-dopa and the higher the daily dosage, the more likely it is that they will develop dyskinesias.

Different motor fluctuations can occur including end-of-dose (wearing off) phenomenon, on-off episodes and freezing. End-of-dose phenomenon develops toward the end of a dosing period where the effects of L-dopa wear off prior to the next dose. On-off episodes occur randomly and unexpectedly. A patient may be functioning well (***on***) one moment and then suddenly have change in functional status becoming quite rigid and immobile (***off***.) These off attacks can last anywhere from minutes to hours. Freezing occurs when a patient suddenly has the sensation that his feet are stuck to the floor. The patient may have difficulty initiating gait or passing through a doorway. Patients may also develop dystonias, which are sustained involuntary contractions of muscles. Dystonias may be painful. This most commonly affects a limb, hand, or foot.

The class of drugs known as the ***COMT inhibitors*** was developed to boost the effect of L-dopa for treatment of Parkinson's disease. The majority of dopamine is metabolized in the brain by two enzymatic systems: MAO-B and COMT (**C**atechol-**O**-**M**ethyl **T**ransferase.) By inhibiting these two metabolic pathways, brain levels of dopamine can be maintained for longer periods of time. This keeps dopamine levels at a steadier level in the brain, thereby reducing motor fluctuations and sustaining longer clinical benefit. COMT inhibitors also block the break down of L-dopa outside of the brain. This makes more L-dopa available to cross the BBB for conversion to dopamine. The first COMT inhibitor available in the United States was tolcapone (Tasmar.) The FDA approved entacapone (Comtan) in late 1999. In general, the COMT inhibitors are well tolerated but like many Parkinson medications, have the potential for side effects. Rarely tolcapone can cause a severe liver problem, which can be fatal. For this reason, Comtan has become the preferred COMT inhibitor. However, for patient's that have not benefited from Comtan or other dopamine boosting agents, Tasmar would be a reasonable medication to consider. COMT inhibitors act in conjunction with L-dopa and must be given with this drug. COMT inhibitors will not improve Parkinson's disease if taken alone. ***Stalevo*** is a combination tablet containing Comtan, levodopa and carbidopa.

Dopamine agonists are chemical agents that mimic the action of dopamine. Unlike L-dopa, dopamine agonists do not need to undergo enzymatic transformation to exert their clinical effects. These agents can be taken orally. They cross the blood-brain barrier and act directly on the dopamine receptor sites. Bromocriptine was the first dopamine agonist. It has been available for Parkinson Disease treatment since 1970 but was not widely used due to the high doses required for clinical benefit, difficulty in titration of dosing, cost and side effects.

Newer dopamine agonists have been developed. These medications have a more specific action on specific dopamine receptors than bromocriptine. Current agents include pramipexole (Mirapex), ropinirole (Requip) and rotigotine patches (Neupro.) Permax (pergolide) was voluntarily removed from the market due to risk of cardiac valvular disease.

Apokyn (apomorphine) is an injectable dopamine agonist. It is quite useful in Parkinson disease for patients that have recurrent, prolonged off times during the day or night. This medication is rapidly acting with a duration of effect for about 90 minutes. This helps patients by allowing them to function during a time that they would otherwise be incapacitated, until their other medications take effect. This medication can be particularly useful in the morning, when PD patients more commonly have significant off time.

The dopamine agonists have been viewed by many clinicians to be a more appropriate first line treatment for Parkinson's disease. The idea is to delay starting L-dopa therapy for as long as possible while maintaining a patient's functional level. Dopamine agonists are also used as additive therapy with L-dopa. They can smooth out the motor fluctuations that occur with L-dopa therapy. This is particularly true for patients with on-off or wearing off episodes. The dopamine agonists have a relatively prominent side effect profile including nausea, low blood pressure, drowsiness, leg swelling, hallucinations, paranoia, nightmares, confusion, and psychosis. It is usually these side effects that limit the usefulness of this class of drugs.

Amantidine (Symmetral) is a drug that can be helpful in Parkinson's disease therapy. Amantidine is thought to help promote dopamine-containing neurons to more easily release their dopamine thereby helping to alleviate Parkinson symptoms. This however is still a matter of dispute. Amantidine is generally safe to use and is commonly started early in the course of treatment of Parkinson's disease. Generally, it loses its effectiveness over a few months although some patients continue to get lasting benefit.

A class of drugs known as "anticholinergics" is frequently used in combination with L-dopa therapy. Acetylcholine is a major neurotransmitter in the brain. Dopamine helps to suppress the effects of acetylcholine. Since there is a brain dopamine deficiency in Parkinson patients, the effects of acetylcholine become more pronounced. The use of anticholinergic compounds can help to control the effects of acetylcholine. Anticholinergics may help to relieve the tremor, rigidity, excessive salivation and sweating that Parkinson patients experience. The anticholinergics can have significant side effects including dry mouth, blurred vision, constipation, difficulty urinating, hallucinations, forgetfulness and confusion. The two most commonly used anticholinergic drugs are trihexyphenidyl (Artane) and benztropine mesylate (Cogentin.)

Selegiline (Eldepryl) is a selective monoamine oxidase-B (MAO-B) inhibitor. Dopamine is broken down (metabolized) in the brain by MAO-B. Selegiline can be used for enhancing the effect of L-dopa by slowing the

metabolism of dopamine. This has the effect of raising brain dopamine levels. By doing so, the total daily dosage of L-dopa can frequently be reduced. This in combination with a dopamine agonist and/or Comtan can reduce or eliminate some of the troublesome side effects seen with higher doses of L-dopa such as confusion, dyskinesias and dystonias. It can also help by smoothing out end-of-dose phenomenon and on-off episodes. The MAO-B inhibitors can occasionally be effective as a first line treatment in early Parkinson's disease. Newer MAO-B inhibitors are being developed. Zelepar is a newly developed, faster acting form of selegiline. The tablet dissolves rapidly in the mouth and is absorbed through the oral tissues, bypassing stomach adsorption.

Azilect (Rasagiline) is the newest MAO-B inhibitor approved by the FDA for clinical use beginning August 2006. Azilect has been shown in studies to be of significantly better benefit, even when used as initial therapy for Parkinson disease, over selegiline. For patients taking Azilect, they must be made aware of the potential for Serotonin Syndrome. This condition may present clinically as a wide range of clinical symptoms. Mild symptoms may consist of rapid heart rate, sweating, twitching or increased tremor. More severe symptoms can include marked blood pressure elevation and body temperature elevations 102-104**°.** In the most severe cases, patients may go into shock. Fortunately, Serotonin Syndrome is very rare.

Non-pharmacologic Therapy

Parkinson's disease not only affects the various motor systems of the body; it also affects a patient's overall functional status. It is important that Parkinson patients do what they can to minimize the impact of their disease on their daily life. Exercise is of major importance and can be in any form such as daily stretching, walking, swimming, bicycling, gardening or any other regular physical activity that allows for some physical conditioning. A daily stretching routine is also beneficial. In earlier stages of Parkinson's disease, some patients are able to play golf or tennis. The important point is that physical *inactivity* can cause accelerated deterioration of a patient's functional abilities.

Diet can play an important role. High protein diets may interfere with L-dopa absorption. It is best to take L-dopa containing medications on an empty stomach or with low protein meals. This can help minimize problems with motor fluctuation that occur in some patients. A high fiber diet with adequate daily fluid intake will help to control constipation. This is a problem that plagues most Parkinson patients.

Physical therapy for gait and balance rehabilitation can be beneficial in patients who have had significant deterioration of balance, walking abilities, and overall functioning. Unless a patient continues at home what he/she was taught in therapy, their condition will again deteriorate making therapy pointless. This therapy must also be combined with some form of regular exercise to be maximally effective. Swallowing difficulty can also be helped to a degree. Speech

therapy can provide a patient with certain maneuvers, head positioning and techniques to minimize the risk of choking or swallowing food/liquids down into the lungs (*aspiration*.)

Daytime drowsiness, sleepiness and frequent naps are a problem. Some of this is from the Parkinson's disease itself but many of the medications can make this problem worse. Patients are encouraged to drink 1-3 cups of regular coffee daily to help combat this. Coffee also helps with control of constipation. Caffeine tablets can be substituted for patients who will not drink regular coffee.

Support groups provide the patient, family and caregivers with the needed educational and emotional support that is frequently lacking. These groups are a good source for up-to-date information on Parkinson's disease and the newest therapies that become available. Patients, family members, caregivers and interested friends should all become involved in their local Parkinson's disease support groups. Parkinson links for national support group information can be found at www.ParkinsonDoctor.com.

Surgical Treatment of Parkinson's disease

Researchers have looked for years for a surgical method that could be used to successfully treat Parkinson's disease. There are three different surgical approaches to treatment of Parkinson's disease: 1-pallidotomy/thalamotomy, 2-brain stimulator implantation, 3-neural transplantation. Surgical treatment is helpful for Parkinson patients that have significant motor fluctuations that are not controlled with medications. These fluctuations include tremor, excessive freezing, dyskinesias, dystonia, and off time. The current primary surgical treatment for Parkinson's disease is deep brain stimulator implantation. ***It is important to note that with surgical treatment of Parkinson's disease, the best that a patient will do is only as good as they are on their best on time on Sinemet.*** Surgery does not reverse the neurodegenerative process. Patients with dementia or other significant psychiatric symptoms are not candidates for surgical therapy.

Pallidotomy was the first surgical therapy used for treatment of Parkinson's disease. In this procedure a highly trained neurosurgeon inserts a small needle electrode deep into the brain into the globus pallidus. The procedure is painless and the patients are fully awake. Using precision localization techniques, the neurosurgeon creates a small lesion at the tip of the electrode, to intentionally destroy a few brain cells. The clinical effect of a pallidotomy is to relieve some of the disabling symptoms of Parkinson's disease. Another similar surgical procedure known as a thalamotomy was also used. Neither of these procedures is used in the current surgical treatment of Parkinson patients.

State-of-the-art therapy for Parkinson's disease now involves deep brain stimulator (DBS) implants. The FDA has approved DBS implantation in patients with intention tremor (essential or familial tremor), Parkinson's disease and

dystonia. Stimulators are effective for severe motor fluctuations. A deep brain stimulator is similar to a heart pacemaker but the electrodes are placed in specific areas of the brain instead of the heart. Deep brain stimulators offer great advantages over pallidotomies and thalamotomies in that it does not involve brain cell destruction. The stimulators can be fine tuned as the Parkinson symptoms progress or change. A stimulator can only regulate one side of the brain therefore two stimulators would need to be implanted if a patient was having disabling symptoms on both sides. The Kinetra stimulator unit was approved in late 2003 by the FDA. This is a single unit that can control 2 sets of electrodes thereby eliminating the need for placement of the second stimulator.

Lastly, there has been an interest in transplantation of dopamine cells into a Parkinson patient's brain. Research in the transplantation of fetal pig cells (dopamine containing nerve cells) has shown some promise in alleviating some of the troublesome clinical symptoms of Parkinson's disease. Some research even suggests that Parkinson's disease may be partially reversed. Research into this area is ongoing and the final conclusions about this procedure's effectiveness are still several years off.

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