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Review Article

Newer Aspects in the Treatment of Parkinson's Diseases

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ABSTRACT

Parkinson's disease (PD) is one of the major neurodegenerative disorders of middle and old age group people. It is characterized by a trio of cardinal symptoms such as muscle rigidity, tremor, and Bradykinesia. It also involves postural deficits and impaired gait, as well as dementia. There is no cure for Parkinson's disease, but medications can help to control some of the symptoms of this disease. This review is aimed to offer a study of treatments of Parkinson's disease. More emphasis is given on modern treatments like - Deep Brain Stimulation (DBS), Gene Therapy etc.

Keywords: Parkinson's disease, rigidity, tremor, bradykinesia, Gene Therapy and Deep Brain Stimulation.

INTRODUCTION

Parkinson's disease is both chronic and progressive. This disease belongs to a group of conditions which called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and a loss of physical movement (akinesia) in extreme cases. In most cases, the first symptom of Parkinson's disease is tremor (trembling) of a limb, especially when body is at rest. The tremor often begins on one side of the body, frequently in one hand.As the disease progresses both sides of the body may be involved and shaking of the head may also occur. Second symptom includes slow movement, difficulty in initiating movement, rigid limbs, a suffering gait, a stopped posture and reduced facial expressions. The third symptom is associated with depression personality changes, dementia, sleep disturbances, speech impairments, and sexual difficulties.[1, 2]

Parkinson's disease is relatively rare overall, but it becomes a common problem of the elderly, affecting about 6% of those over the age of 65. In the United States about 500,000 to 1,000,000 people are believed to suffer from Parkinson's disease, with about 50,000 new cases are reported annually. The disorder of this disease is more common in men than women. The average age of people suffer this disease is about 60, rarely it occurs before age 40, but increasingly diagnosed with aging.[1]

Causes of Parkinson's disease are not fully known but mainly three factors – Genetic, Toxins and Head trauma are related to PD. Genetic factors are involved in susceptibility and there may be contributions from a variety of behaviors. For example, it has been suggested recently that people who drink coffee and tea are less likely to suffer from Parkinson's than those who drink little of these caffeinated beverages.

PD is the most common cause of chronic progressive Parkinsonism. It refers to the syndrome of tremor rigidity, bradykinesia and postural instability. PD is also called "Primary Parkinsonism" or "idiopathic PD" (classically meaning – having no known cause although this term is not strictly true in light of the plethora of newly discovered genetic mutation). The "Secondary" case may result from toxicity most notably of drugs, head trauma, or other medical disorders[2].

In some cases, it would be in correct to say that the cause is "unknown" because a small portion is caused by genetic mutations. It is possible for a patient to be initially diagnosed with Parkinson's disease but then to develop additional features, requiring revision of the diagnosis.[3]

There are other disorders that are called Parkinson – plus diseases. These are include: multiple system atrophy (MSA), progressive supranu clear palsy (PSP) and corticobasal degeneration (CBD). Some include dementia with Lewybodies (DLB) – while idiopathic Parkinson's disease patients also have

Lewybodies in their brain tissue, the distribution is denser and more widespread in DLB. The relationship between Parkinson's disease, Parkinson disease with dementia (PDD), and dementia with lewybodies (DLB) might be most accurately conceptualized as a spectrum, with a discrete area of overlap between each of the three disorders. The cholinester are inhibiting medications have shown preliminary efficacy in treating the cognitive, psychiatric, and behavioral aspects of the disease of both PD and DLB. The natural history and role of Lewy bodies is little understood.[2]

These Parkinson – plus disease may progress more quickly than typical idiopathic Parkinson disease. If cognitive dysfunction occurs before or very early in the course of the movement disorder, then DLBD may be suspected. Early postural instability with minimal tremor, especially in the context of ophthalmoparesis, should suggest PSP. Early autonomic dysfunction, Including erectile dysfunction and syncope, may suggest MSA. The presence of extreme asymmetry with patchy cortical cognitive defects such as dyspharia and apraxeas (especially with "alien limb" phenomena) should suggest CBD.[2]

The usual anti – Parkinson's medications are typical either less effective or completely in effective in controlling symptoms. Patient may be enquisitely sensitive to neuroleptic medications like haloperidol, for this reason correct differential diagnosis is important.

Parkinson's disease affects movement producing motor symptoms. [4] Non-motor symptoms include autonomic dysfunction, cognitive and neurobehavioral problems and sensory and sleep difficulties, which are also common but are under-appreciated.[4]

PATHOPHYSIOLOGY

The major neuropathologic findings in Parkinson's disease are a loss of pigmented dopaminergic neurons in the substantia nigra (Literally "black Substance") and the presence of Lewy bodies. The loss of dopaminergic neurons occurs most prominently in the Ventral lateral substantianigra. Approximately 60- 80% of dopaminergic neurons are lost before motor signs Parkinson disease emerge. These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway.[2, 5]

The direct pathway facilitates movement and the indirect pathway inhibits movement. Thus the loss of these cells leads to a hypokinetic movement disorder.

There are four major dopamine pathways in the brain. These are the nigrostriatal pathway, the mesocortical pathway, the mesolimbic pathway and the tuberoinfundibular pathway. Nigrostriatal pathway medicates movement and this is the most conspicuously affected in early Parkinson's disease.[2]

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha- synuclein bound to ubiquitin in the damaged cells. The alpha – synuclein – ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of this disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles – the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha - synuclein in animal models. [6]

Execessive accumulation of iron are toxic to nerve cells and are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanins in the effected neurons of the substantia -nigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species.[7]

Iron also includes aggregation of synuclein by oxidation mechanisms [8]. Similarly, dopamine and the byproducts of dopamine production enhance alpha – synuclein aggregation. The precise mechanism whereby such aggregates of alpha – synuclein damage. The cells are not known. A transgenic mouse model of Parkinson's has been generated by introduction of human wild – type alpha synuclein into the mouse genome under control of the platelet – derived growth factor – β promoter.[9]

A recent study of Parkinson's disease reveals specialized calcium channels that allow substantia nigra neurons, but not most – neurons, do repetitively fire in a "pacemaker" like pattern. The consequent flooding of calcium into these neurons may aggravate damage to mitochondria and may cause cell death.[2]

- **TREATMENT:**

Parkinson's disease is a chronic disorder that requires broad – based management including patient and family education, support group service, general wellness maintenance physiotherapy, exercise and nutrition.[3]

- **LEVODOPA** :

The most effective Parkinson's drug is levodopa, which is a netural substance in the body when taken by mouth in pill form, it passes into the brain and l-dopa transformed into dopamine in the dopaminergia neurons by L – aromatic amino acid

decarboxylase (often known by its former name dopa-de carboxylase.). Only 1-5% of L – dopa enter the dopaminergic neurons, the remaining L-dopa is often metabolized to dopamine elsewhere, causing a wide variety of side effects, due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa and eventually becomes counterproductive. Levodopa is combined with carbidopa to create the combination drug, sinemet'. The carbidopa protects levodopa from premature conversion to dopamine outside the brain. Indoing that, it also prevents nausea Carbidopa and benseraizide are dopa decarboxylase inhibitors. They help to prevent the metabolism of L-dopa before it reaches the dopaminergic neurons and these are generally given as combination preparations of carbidopa/levodopa (co-careldopa)(e.g sinemet, pareopa) and benserazide/levodopa(co-beneldopa) (e.g Madopar). There are also controlled release version of sinemet and Madopar that spread out the effect of the L-DOPA. Dvodopa is a combination of Levodopa and Carbidopa, dispersed as a Viscous gel. Another drug, stalevo (Carbidopa, Levodopa and entacapone), is also available for treatment.[2, 10]
As the disease progresses, the benefit from levodopa may become less stable, with a tendency to wax and wane. This then requires medication adjustments. Levodopa side effects include involuntary movements that called dyskinesia. There resolve with dose reduction, but sometimes at the expense of reduced Parkinsonism control. Like other Parkinson's drugs it may also lower blood pressure when standing.[10]

- **DOPAMINE AGONISTS :**

These drugs aren't changed into dopamine. Instead, they mimic the effects of dopamine in the brain and cause neurons to react as through dopamine is present. They are not nearly as effective in treating the symptoms of Parkinson's disease.[10]
This class includes pill forms of dopamine agonists, such as bromocriptine, pergolide, pramipexole, ropinirole, piribedil, cabergoline, apomorphine, and lisuride are moderately effective.
The side effects of dopamine agonists include hallucinations, sleepiness, water retention and low blood pressure when standing. These medications may also increase risk of compulsive behaviors. Such as hypersexuality, compulsive gambling and compulsive overeating. [10] Dopamine agonists can be useful for patients experiencing on-off fluctuations and dyskinesia as a result of high doses of L-Dopa.[2]

- **MAO-B Inhibitors**

This types of drugs, including selegiline (Eldepryl) and rasagiline (Azilect) help to prevent the breakdown of both naturally occurring dopamine and dopamine formed from Levodopa. They do this by inhibiting the activity of the enzyme monoamine oxidase B (MAO B) an enzyme that metabolism dopamine in the brains.
The side effects are rare but may include confusion, headache, hallucinations and dizziness.[10]

- **Catechol O-methyltransferase (COMT) Inhibitors**

These drugs prolong the effect of carbidopa – levodopa therapy by blocking an enzyme that breaks down Levodopa.
Tolcapone(Tasmar) inhibits the COMT enzyme and it has been linked to liver damaged and liver failure. So it's normally used only in people who are not responding to other therapies. Entarapone (Comtan) does not cause liver problems and is now combined with carbidopa and Levodopa in a medication called Stalevo. It may worsen other Levodopa side effects, such as involuntary movements (dyskinesias), nausea, confusion or hallucinations. It also may cause urine discoloration.[10]

- **ANTICHOLINERGICS**

These drugs have been used for many years to help control the tremor associated with Parkinson's disease. A number of anticholinergic drugs, such as Benztropine (Congentin) and trihexyphenidyl are available. Their modest benefits are often offset effects such as impaired memory confusion, constipation, dry mouth & eyes and impaired urination.

- **GLUTAMATE (NMDA) BLOCKING DRUGS**

Amantdine (symmetrel) is prescribed to provide short-term relief of mild ,early- stage of Parkinson's disease. It also may be added to carbidopa Levodopa therapy for people in the later stages of Parkinson's disease, especially if they have problem with involuntary movements (Dyskinesia) induced by Carbidopa – Levodopa.
The side effects are a purple mottling of the skin and sometimes hallucinations. [10]

- **CABERGOLINE**

Cabergoline is also known by the brand names Dostiner and Cabaser. Cabergoline is a dopamine agonist primarily stimulates the D_2 receptor activity. It has a very long half – life.[11]
Besides being used for the treatment of Parkinson's Disease, cabergoline is also used for the treatment of hyperprolactinemia and also exerts antidepressant effects[12].

- **Physical Therapy**

Exercise is important for general health, but especially for maintaining function in Parkinson's

disease. Physical therapy may be advisable and can help to improve mobility, range of motion and muscle tone.[10]

- **Chinese Medicine**

The characteristic symptoms of Parkinson's appeared in ancient Chinese medical tests that described trembling of the hands and shaking of the head syndroms in which elderly patients suffer from spontaneous shaking or from other muscular manifestations such as paralysis or tonic spasm , are thought to be result of yin deficiency of the kidney and liver leading to generation of "internal wind".

One of the most commonly used formulations for treating yin deficiency with aging is Rehmannia Six Formula (Liuwei Dihuang Wan), with key tonic herbs rehmannia and cornus. There are also several wind-inhibiting substances recommended by Chinese Herbalists. The main plant- based remedy is gastrodia tuber (other include uncaria and tribulus), while most of the substances are of animal origin, including scorpion, centipede, earthworm, antelope horn and silkworm. The persistence and progression of the disease may be attributable to "Phelegm obstruction of the channels". According to this concept, a residue from food essence accumulates in the channels (blood vessels, meridians) and "fixes" the wind so the symptoms persist over a long period of time. Herbs used to resolve this problem of phlegm obstruction include arisaema, pinellia, and acorus (botanically related), silkworm and gastrodia are also considered for both calming wind and clearing phlegm obstruction.

Herb therapy, acupuncture therapy and antioxidant therapies have been reported to show benefits for some patients suffering from Parkinson's disease.[1]

MODERN TREATMENTS.

- **Gene Therapy**

The very current investigation is gene therapy. This involves using a non-infectious Virus to shuttle a gene into a part of the brain called the subthalamic nucleus (STN). The gene used leads to the production of an enzyme is called glutanui and decarboxylase (GAD). This catalyses the production of neurotransmitter called GABA.[13]

GDNF acts as a direct inhibitor the overactive cells in the STN.

GDNF infusion involves the infusion of GDNF (glial – derived neurotrophic function) into the basal ganglia using surgically implanted catheters. Via a series of biochemical reactions, GDNF stimulates the formation of L-dopa. GDNF therapy is still in development.[2]

- **Fetal Tissue Transplantation :**

The use of fetal stem cell transplantation to treat Parkinson's disease is not widely available and research is in its infancy. Medical and ethical opinion is strongly divided over the issue of issuing fetal tissue to stimulate the dopaminergic neurons in patients suffering from Parkinson's disease.

Rersearch and studies into the benefits of fetal stem cell transplantation have produced mixed results. A number of experiments have shown that grafted cells can survive and function effectively in the mild-brain regions of the recipients, while it also improves movement initiation and rigidity.[14, 15]

- **Neuroproductive Treatments**

Neuroprotective treatments are at the fore front of PD research, but are still under clinical scrutiny. These agents could protect neurons from cell death induced by disease presence resulting in slower progressive of disease. Agents currently under investigation as neuroprotective agents induced anti-apoptotic drugs (CEP 1347 & CTCT 346) Lazaroids, bioenergetics, antiglutametergic agents and dopamine receptors.[16]

- **Neural Transplantation**

The first prospective randomized double – blind sham-placebo controlled trial of dopamine – producing cell transplants failed to show an improvement in quality of life, although some significant clinical improvements were seen in patients below the age of 60. [17][18]

A significant problem was the excess release of dopamine by the transplanted tissue, leading to dystorias.[18]

Research in African green monkeys suggests that use of stem cells might in future provide a similar benefit without inducing dystorias.[19]

- **Deep Brain Stimulation :**

Deep brain stimulation (DBS) is a surgical procedure which is used to treat a variety of disabling neurological symptoms – most commonly the debilitating symptoms of Parkinson's disease such as tremor, rigidity, stiffness, slowed movements. The procedure is also used to treat essential tremor, a common neurological movement disorder. Now, the procedure is used only for those patients whose symptoms cannot be adequately controlled with medications.

The history of DBS in movement disorder can be traced to the 1950s and 60s when early investigation observed that the high frequency stimulation of the neural intermediate nucleu (Vim) of the thalamus, performed intraoperatively for clinical localization abolished tremor.[20][21] This led to the investigation of the efficiency of chronic stimulation of the Vim neclues as a treatment for tremor disorders. Chronic DBS of VIM was

reported to be an effective treatment for tremor of PD and essential tremor in the early 1990's.[22-24]

Vim DBS in PD prompted the application of this technique as the target for pallidotomy, i.e. the porteroventral part of globus pallidus pars intera (GPI) as well as in the subthalamic nucleus (STN).[25, 26] Many reports have now established that DBS of GPI and STN are both effective and safe in treating medically refractory motor fluctuations and LIDS in PD.[27]

The exact mechanism of the action of DBS is unknown. As the clinical effects of the DBS of Vim and GPI on tremor and Parkinsonism are similar to lesioning. It is proposed that DBS has inhibitory rather than excitation effects on the functions of all its target nuclei. Depolarization block of the neurons of the target nuclei is generally considered to be the most likely mechanism of this inhibition. It has also been proposed that pathological such as tremor related activity in the target neurons may be disrupted (jamming) by high frequency stimulation.[28]

DBS uses a surgically implanted battery – operated medical device is called a neurostimulator. It is similar to a heart pacemaker and approximately it looks like a stopwatch. It delivers electrical stimulation to targeted areas in the brains that control movement, blocking the abnormal nerve signals that cause tremor and PD symptom.

Before DBS procedure, a neurosurgeon uses magnetic resources imaging (MRI) or computed tomography (CT) scanning to identify and locate the exact target within the brain electrical nerve signals generate the PD symptoms. Some surgeons may use micro electrode recording which involves a small wire that monitor the activity of nerve cells in the target area – to more specifically identify the precise brain target that will be stimulate. Generally, there targets are the thalamus, subthalamus, nucleus, and globus pallidus.

This DBS system consists of there components – the lead, the extension, and the neuronstimulator (The lead also called an electrode) is a thin, insulated wire. It is inserted through a small opening in the skull and implanted in the brain. The HP of the electrode is positioned within the targeted brain area.

The extension is an insulated wire that is passed under the skin of the head, neck and shoulder. It connects the lead to the neuro-stimulator.

The third component is the neurostimulator (the "battery pack"). It is usually implanted under the skin near the collar bone. In some cases it may be implanted lower in the chest or under the skin over the abdomen.

Once the system is in place , electrical impulses are sent from the neurostimulator up along the extension wire and the lead and into the brain. These impulses interfere with and block the electrical signals that cause PD symptom.[29]

Deep brain stimulation treatment may improve movement skills and quality of life for patients with advanced Parkinson's disease over other medical therapies. Though it may also have a higher risk of serious adverse events, according to an article released on January 6,2008 in Jama.[30]

- **Alternative Treatments**

Nutrients have been used in clinical studies and are used by people with Parkinson's disease in order to partially treat Parkinson's disease or to slow down its deterioration. The L-dopa precursor L-tyrosine was shown to relieve an average of 70% of symptoms.

Ferrous iron, the essential co factor for L-dopa biosynthesis was shown to relieve between 10% and 60% of symptoms in 110 out of 110 patients.[31, 32]

More limited efficiency has been obtained with the use of THAT,NADH and pyridoxine – coenzyme precursors involved in dopamine biosynthesis.[33]

Vitamin C and Vitamin E in large doses are commonly used by patients in order to theoretically reduce the cell damage that occurs in PD. The cause is that the enzymes superoxide dismutase and catalase require these vitamins in order to nullity the superoxide anion a toxin commonly produced in damaged cells. However, in the randomized controlled trail , DATA TOP of patients with early PD, no beneficial effect for Vitamin E composed to placebo was seen. [34] Coenzyme Q10 is used more recently for similar reasons, Mito Q is a newly developed synthetic substance that is similar in structure and function to co-enzyme Q10. Most of these therapies are covered in Dr. Laurie Mischley's Natural Therapies for Parkinson's Disease.[35]

- **CONCLUSION**

All the treatments which are discussed in this article show benefits for some patients suffering from Parkinson's disease. Among those treatments deep brain stimulation, gene therapy are very modern treatments and provide a new approach for the control of symptoms in advanced Parkinson's disease. These new modern therapies are still in development.

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