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A REVIEW ON NEWER APPROACHES IN PARKINSON'S DISEASE MANAGEMENT

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ABSTRACT

Parkinson's disease is a degenerative disorder of the central nervous system mainly affecting the motor system. It is a neurodegerative disorder which is caused by lack balance between dopamine and acetylcholine levels in brain. It is characterized by chronic and progressive movement disorder. Nearly one million people in the US are living with Parkinson's disease. The cause is unknown and although there is presently no cure and there are treatment options such as medication and surgery to manage its symptoms.Patients with parkinsons disease explore bradykinesia, rigidity, tremor, postural instability. mutations involving genes that play a role in imbalacing of dopamine functions. Parkinson's has developed at an early age individuals with mutations in genes for parkin, PINK1, LRRK2, DJ-1 and glucocerebrosidase. several newer trends are existing now to treat the conditions like stem cells therapy, Gene therapy, deep brain stimulation technique has been creating new directions for Parkinsons research. In Deep brain stimulation uses an electrode surgically implanted into part of the brain. gene therapy making cells produce a protein that they normally do not produce that might improve a particular condition. The genes that provide specific genetic instructions that cells use to produce a desired protein. It relies on transporting small pieces of genetic material into the targeted brain cells and desire improve targeted cells function.

KEYWORDS: Bradykinesia, Rigidity, Tremor, Mutations, Genes.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative brain disorder that progresses slowly in most of the people. In shortly parkinsons person's brain slowly stops producing a neurotransmitter called dopamine. A person has less and less ability to regulate their movements, body and emotions. Parkinson's disease (PD) is a degenerative disorder of the central nervous system that belongs to a group of conditions called movement disorders. It is both chronic, meaning it persists over a long period of time and progressive, meaning its symptoms grow worse over time. As nerve cells (neurons) in parts of the brain become impaired or die, people may begin to notice problems with movement, tremor, stiffness in the limbs or the trunk of the body, or impaired balance.[1]

Tremor or Shaking

These patients we can observe a slight shaking or tremor in fingers, thumb, hand, chin or lip.

Loss of normal Handwriting

The Parkinsons patients write words on a page has changed, such as letter sizes are smaller and the words are crowded together. A sudden change in handwriting is often itself indicates sign of Parkinson's disease.[2]

Loss of Smell

The patients have more trouble smelling foods like bananas, dill pickles or licorice.

Insomnia Troubles

Sudden movements in body due to lack of sleep associated stress.

Trouble Moving or leg pain

The person he won't move but he stick to the floor. but the swelling in legs makes condition to be more trouble.

Constipation

The bowel movements completely reduced due to lack of consumption of fiber food and the patients with more stress.

Low sound: The people will speak low voice Sometimes people are losing their hearing due tom parkinsons condition.

Masked Face: Parkinson's patients we can observe having a serious, depressed or mad look on your face more often. The person with serious-looking face is called masking.

Dizziness or Fainting
They may Feel dizzy or fainting can be signs of low blood pressure and can be linked to Parkinson's disease.

Stooping
The person to be stooping, leaning or slouching when they stand, it could be a sign of Parkinson's disease.[3]

Major Motor Symptoms of PD

- Shaking or tremor
- Slowness of movements (bradykinesia)
- Stiffness or rigidity of the arms, legs or trunk
- Trouble with balance and possible falls, also called postural instability.

Pathophysiology Of Parkinsons Disease

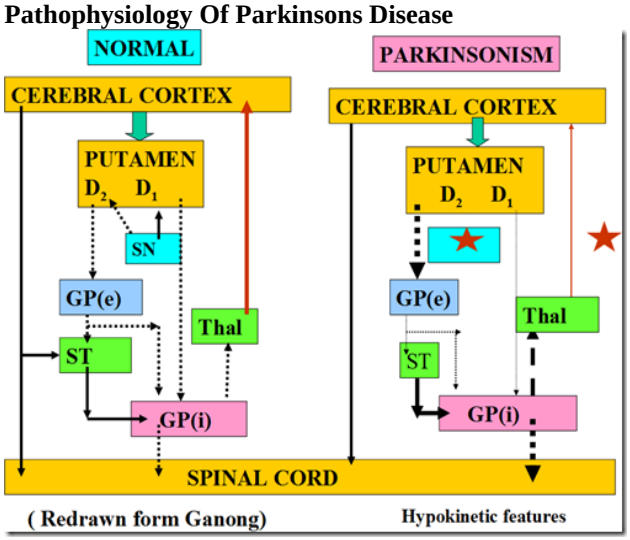

Fig: Pathophysiology Of Parkinson's Disease

Epidemiology

- As many as one million Americans live with Parkinson's disease.
- Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this count does not reflect the thousands of cases that go undetected.
- An estimated seven to 10 million people worldwide are living with Parkinson's disease.
- Incidence of Parkinson's increases with age, but an estimated four percent of people with PD are diagnosed before the age of 50.[3]

Causes for the disease
Genetics. Scientists have identified several genetic mutations associated with PD, including the alpha-synuclein gene and many more genes have been tentatively linked to the disorder. **Mitochondria**: Mitochondria are the energy-producing components of the cell and abnormalities in the mitochondria are major sources of free radicals and molecules that damage membranes, proteins, DNA and other parts of the cell. This damage is often referred to as oxidative stress.

Other genes linked to PD include parkin, DJ-1, PINK1 and LRRK2. DJ-1 and PINK1 cause rare, early-onset forms of PD.[4]

symptoms of Parkinsons disease
The primary symptoms of PD are:
Tremor. The tremor associated with PD has a characteristic appearance. Typically, the tremor takes the form of a rhythmic back-and-forth motion at a rate of 4-6 beats per second. It may involve the thumb and forefinger and appear as a "pill rolling" tremor. Tremor often begins in a hand, although sometimes a foot or the jaw is affected first.

Rigidity. Rigidity, or a resistance to movement, affects most people with PD. The muscles remain constantly tense and contracted so that the person aches or feels stiff. The rigidity becomes obvious when another person tries to move the individual's arm, which will move only in ratchet-like or short, jerky movements known as "cogwheel" rigidity.

Bradykinesia. This slowing down of spontaneous and automatic movement is particularly frustrating because it may make simple tasks difficult.The person cannot rapidly perform routine movements.[5]

Postural instability. Postural instability, or impaired balance, causes affected individuals to fall easily.

A number of other symptoms may accompany with PD
Depression: people lose their motivation and become dependent on family members. **Emotional changes**: Some people with PD become fearful and insecure, while others may become irritable.

Difficulty with swallowing and chewing
Muscles used in swallowing may work less efficiently in later stages of the disease.Food and saliva may collect in the mouth and back of the throat, which can result in choking or drooling.

Speech changes: individuals with PD have speech difficulties that may be characterized as speaking too softly or in a monotone. Some may hesitate before speaking, slur, or speak too fast.

Urinary problems or constipation: In some people with PD, bladder and bowel problems can occur due to the improper functioning of the autonomic nervous system.

Skin problems
In PD, the skin on the face may become oily, particularly on the forehead and at the sides of the nose.

Sleep problems
Sleep problems are common in PD and include difficulty staying asleep at night, restless sleep, nightmares and

emotional dreams and drowsiness or sudden sleep onset during the day.

Dementia or other cognitive problems
Some people with PD may develop memory problems and slow thinking. Memory, social judgment, language, reasoning, or other mental skills may be affectes in patients.

Orthostatic hypotension
Orthostatic hypotension is a sudden drop in blood pressure when a person stands up from a lying-down or seated position. This may cause dizziness, lightheadedness and in extreme cases, loss of balance or fainting.

Muscle cramps and dystonia
The rigidity and lack of normal movement associated with PD often causes muscle cramps, especially in the legs and toes.

Pain. Many people with PD develop aching muscles and joints because of the rigidity and abnormal postures often associated with the disease.[5]

Fatigue and loss of energy
Many people with PD often have fatigue, especially late in the day. Fatigue may be associated with depression or sleep disorders.

Sexual dysfunction
Because of its effects on nerve signals from the brain,PD may cause sexual dysfunction.

Non-motor symptoms in Parkinson's disease include
- Cognitive changes, slowing of thought, language and memory difficulties
- personality changes, dementia. Hallucinations and delusions, Orthostatic hypotension
- Sleep disorders such as insomnia, excessive daytime sleepiness (EDS), rapid eye movement behavior disorder (RBD), vivid dreams, talking and moving during sleep, restless legs syndrome (RLS)/periodic leg movements disorder (PLMD)
- Constipation and early satiety (a feeling of fullness after eating small amounts)
- Pain, Fatigue, Loss of vision
- Excessive sweating, especially of hands and feet, with no or little exercise
- Increase in dandruff (seborrhea dermatitis), oily skin
- Urinary urgency, frequency and incontinence**,** Loss of sense of smell
- Sexual problems**,** Weight loss or weight gain

Mixed Motor And Non-Motor Symptoms in Parkinsons Disease includes
The same PD symptoms that occur in muscles of the body, tremors, stiffness and slow movement can occur in the muscles used in speaking and swallowing, results in the following changes:
- Soft voice
- Drooling or excessive saliva due to slow swallowing
- Speech and swallowing problems.[4]

Stages of parkinsons disease
According to the guidelines of Hoehn and Yahr Staging of Parkinson's Disease
Stage one -- symptoms on one side of the body only (unilateral).
Stage two -- symptoms on both sides of the body. (bilateral).
Stage three -- balance impairment. Mild to moderate disease. Physically independent.
Stage four -severe disability, but still able to walk or stand unassisted.
Stage five – wheelchair-bound or bedridden unless assisted.

Atypical parkinsonism should be considered particularly it includes
- in patients with poor dopamine responsiveness
- early loss of balance
- prominent dementia
- rapid onset or progression
- prominent autonomic dysfunction
- little or no tremor

Atypical forms of Parkinsonism include
- Medication-induced Parkinsonism
- Progressive Supranuclear Palsy (PSP)
- Corticobasal Degeneration (CBD)
- Multiple System Atrophy (MSA)
- Vascular Parkinsonism
- Dementia with Lewy Bodies (DLB)

Recent approaches in Parkinson's Treatment
- Gene therapy
- Stem cells research
- Deep brain stimulation technique

Stem cells research
The California-based company, the International Stem Cell Corporation (ISCO), has announced the first clinical trials of a stem cell treatment for Parkinson's. They hope that to grow new brain cells from stem cells and use these to replace the cells that are lost and further maintain the dopamine levels in the brain.[6]

Deep brain stimulation technique
Deep Brain Stimulation
Deep brain stimulation, or DBS, uses an electrode surgically implanted into part of the brain[9], typically the subthalamic nucleus or the globus pallidus.Similar to a cardiac pacemaker, a pulse generator (battery pack) that is implanted in the chest area under the collarbone sends finely controlled electrical signals to the electrode(s) via a wire placed under the skin.When turned on using an external wand, the pulse generator and electrodes painlessly stimulate the brain in a way that helps to block

signals that cause many of the motor symptoms of PD. DBS can be used on one or both sides of the brain.If it is used on just one side, it will affect symptoms on the opposite side of the body. DBS is primarily used to stimulate one of three brain regions: the subthalamic nucleus, the globus pallidus interna, or the thalamus.Stimulation of either the globus pallidus or the subthalamic nucleus can reduce tremor, bradykinesia and rigidity.[9] Stimulation of the thalamus is useful primarily for reducing tremor.

Deep brain stimulation (DBS) is a surgical procedure used to treat several disabling neurological symptoms most commonly the debilitating motor[10] symptoms of Parkinson's disease (PD), such as tremor, rigidity, stiffness, slowed movement and walking problems.DBS uses a surgically implanted, battery-operated medical device called an implantable pulse generator (IPG) similar to a heart pacemaker and approximately the size of a stopwatch to deliver electrical stimulation to specific areas in the brain that control movement, thus blocking the abnormal nerve signals that cause PD symptoms.

Gene therapy background

Gene therapy in Parkinson disease consists in the creation of new cell that produces a specific neurotransmitter (dopamine), protect the neural system, or the modification of gene's that are related to the disease. First of all, currently there is no cure for this disease. Secondly, some genes have been identified which can modulate the neuron phenotype or act as neuroprotective agents. Also, the environment of the brain cannot afford repeated injections into the region where the substantia nigra meets the striatum, the nigrostriatum.Therefore, gene therapy could be a single treatment appealing, viral vectors used in the therapy are diffusible and capable to do transduction of the striatum.[7]

Gene therapy bases

The concept of the gene therapy is to create new generations of cells that produce particular neurotransmitter (dopamine) and then transplant these cells to the patients with PD. Also, the use of embryonic dopaminergic cells cannot be used because these cells are difficult to obtain and modifications of cell can only be made on somatic cells not germline. With the modifications of the transplanted cell, there can be a change in the expression of the genes.[8]

Gene therapy approaches

Disease modifying approaches

The first one is the neurotrophic factors gene delivery. In this therapy GNDF or NTN are used to protect the system. GNDF is a factor of the TGFß superfamily, is secreted by astrocytes (glia cells that are in charge of the survival of the midbrain dopaminergic neurons) and is homologous to NTN,persephin and artemin. There have been explored several viral vector-based gene delivery system that interfere with α- synuclein expression, and they depend on the interference of the RNA (destabilizing the α-synuclein RNAm) and/or the block the protein translation (using short hairpin RNA or micro RNA directed against the α-synuclein RNAm sequence.

Gene therapy for Parkinson's disease

It means of making cells produce a protein that they normally do not produce that might improve a particular condition. The technique inserts genes that provide specific genetic instructions that cells use to produce a desired protein.

Gene therapy relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells. Because human bodies have developed a number of enzymes that breakdown unprotected DNA, most gene therapies use some sort of "protective envelop", called a **vector,** to carry the genetic material and deliver the gene to targeted cells.

Treatment strategy	**Gene(s)**	**Vector**	**Completed studies**	**Ongoing or Enrolling studies**
Increase dopamine	AADC	AAV-2	Phase 1	Phase 1 to start in 2013
	AADC, TH, & GCH-1	Lentivirus		Phase 1 & 2 in progress
Alter excitatory activity	GAD	AAV-2	Phase 1 & 2	
Growth factors	GDNF	AAV-2	-	Phase 1 to start in 2012
	Neurturin	AAV-2	Phase 1 & 2	Second Phase 2 in progress

Medications to Treat the Motor Symptoms of Parkinson's Disease

- **Levodopa/Carbidopa.** The cornerstone of therapy for PD is the drug levodopa (also called L-dopa).
- **Dopamine agonists**: These drugs, which include apomorphine, pramipexole, ropinirole, and rotigotine, mimic the role of dopamine in the brain.
- **MAO-B inhibitors**: When selegiline is given with levodopa, it appears to enhance and prolong the response to levodopa and thus may reduce wearing-off.
- Selegiline is usually well-tolerated, although side effects may include nausea, orthostatic hypotension, or insomnia.
- **COMT inhibitors**: COMT inhibitors can decrease the duration of "off periods" of one's dose of levodopa.
- **Amantadine**. This antiviral drug can help reduce symptoms of Parkinsons disease**.**
- **Anticholinergics**. These drugs, which include trihexyphenidyl, benztropine and ethopropazine, decrease the activity of the neurotransmitter acetylcholine and can be particularly effective for tremor.

Category	Generic name,dose	Brand name
Drugs that increase brain levels of dopamine	Levodopa/carbidopa 25-100 mg 25-250 mg 3-4 times per day	Parcopa, Sinemet
Drugs that mimic dopamine (dopamine agonists)	Apomorphine Pramipexole: 0.125 mg 0.25 mg 1.0 mg 1.5 mg Ropinirole. 0.25 mg 0.5 mg 1.0 mg 2.5 mg Rotigotine	Apokyn Mirapex Requip Neupro
Drugs that inhibit dopamine breakdown (MAO-B inhibitors)	Rasagiline Selegiline (deprenyl)	Azilect Eldepryl, Zelapar
Drugs that inhibit dopamine breakdown (COMT inhibitors)	Entacapone Tolcapone	Comtan Tasmar
Drugs that decrease the action of acetylcholine (anticholinergics)	Benztropine Ethopropazine Trihexyphenidyl	Cogentin Parsidol Artane
Drugs with an unknown mechanism of action for PD	Amantadine	Symmetrek

Surgery

Pallidotomy and Thalamotomy

The most common lesion surgery is called pallidotomy. In this procedure, a surgeon selectively destroys a portion of the brain called the globus pallidus. Pallidotomy can improve symptoms of tremor, rigidity and bradykinesia, possibly by interrupting the connections between the globus pallidus and the striatum or thalamus.[8]

CONCLUSION

We hope that the new approaches will bring the effectiveness in treatment of parkinsons patients and it will give newer way to research. Gene therapy restore dopaminergic neurons through the use of growth factors or alternatively increase the availability of enzymes required for dopamine synthesis. deep brain stimulationassociated with reducing tremor. It is hoped that gene therapies and deep brain stimulation techniques

and stem cells research will relies to be effective improved treatment options for people with Parkinson's disease in the near future.

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