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Parkinson's disease: A review article

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Abstract
Parkinson's is one of the most horrendous disease affecting 1% of the adult population above the age of 60 and 4% over the age 85 [1]. This disease is chronic and progressive in neurodegeneration causing dopaminergic neurons in *Substantia nigra* region of the mid brain to die which ultimately leads to decrease in dopamine production in our brain. Though any direct cause of this disease has not been identified yet, but many genetic mutations and environmental factors are found to be related to it. The diagnosis depends on family genetic history and disease symptoms. Dopamine is a neurotransmitter which controls certain notable functions of body including movement, memory, sleep, attention and learning. Due to plummeted production of dopamine, a Parkinson's patient encounters several symptoms like tremor, bradykinesia, rigidity, postural instability.

Keywords: Dopamine, Neurodegeneration, Parkinson

Introduction
Rest tremor or shaking palsy is seen dominant in Parkinson's disease that is greater on the side of initial involvement. These tremors are slow and interferes during movements like drinking from cup or eating from spoon [2]. Tremors were seen to slow down when patient is in continuous movement. There is a lack of balance and stiffness of body parts which obstructs patient's normal movement. Bradykinesia is a symptom which manifests in several ways causing decrease in motor coordination.
Certain secondary symptoms associated with Parkinson's include drooling, swallowing difficulty, speaking difficulty, visual problems, urinary problems, sexual dysfunctions and weight loss [2]. According to research, the cause of Parkinson's disease was found to be due to both environmental and genetic factors. Though environmental factors have not been identified yet to directly cause the disease, but they can trigger the upregulation of rogue genes involved in Parkinson's. Exposure to certain environmental factors like pesticide, fungicide, MPTP (*methyl-phenyl-tetrahydropyridine),* herbicide, fungicide can increase an individual's risk of the disease [6]. Studies published by National Institute of Environmental Health Sciences in 2011, reported that occupational users of two pesticides "rotenone" and "paraquat" had found to develop the disease 2.5 times more than non –users [5].
Unlike environmental factors, genetic errors and mutations are directly associated with Parkinson's disease indeed. Many chromosomal loci named "PARK" are linked to this disease. A single mutation caused in the genes of these loci can either lead to Parkinson's or enhance the risk factor of the same. Among these only six regions contain genes that unequivocally cause monogenic PD on mutation [3]. Some of these are autosomal dominant and others are autosomal recessive in inheritance.

Some autosomal dominant genes involved in PD are
SNCA (Alpha- synuclein; PARK1): The missense mutation A53T in gene alpha-synuclein which is located in long arm of chromosome 4q21 causes early onset of PD along with rapid progression of dementia and psychiatric disturbances. Four additional mutations that are A30P, E46K, G51D and H5OQ have also been found in families with dominantly inherited PD [1].

LrrK2 (PARK8): This is a large gene consist of 51 exons [3]. Today, more than 80 mutations in this gene is linked with PD accounting for 10% familial PD and significant number of sporadic PD. LrrK2 is mainly associated with formation of lewy body and aggregation of tau protein which causes improper functioning of neurons(1).

Vps35 (PARK17): A mutation D620N in this gene cause late onset, autosomal dominant PD. The average age of onset of disease is around 51 years with increased rates of tremors, bradykinesia and postural instability [1].

Some autosomal recessive genes involved in PD are

Parkin (PARK2): This gene has a role in mechanism of proteasome. Mutation causes loss of its function which is ubiquitination of protein by E3 ubiquitin ligase. These causes toxic build up proteins. Formation of these in neurons have crucial role in pathogenesis of PD [1].

Pink1 (PARK6): Homozygous missense mutation G309D and homozygous nonsense mutation W437X in this gene were detected to cause PD. Patients with PINK1 mutations have an early onset of PD, with slow progression and with often atypical features such as dystonia, anxiety and depression [1]. This gene acts in a common pathway of Parkin for sensing and selectively eliminating damaged mitochondria from the mitochondrial network [3] and is upstream activator of parkin [1].

Dj-1 (PARK7): This gene is protective against oxidative stresses. More than ten mutations have been described in this gene that can cause autosomal recessive juvenile Parkinson's. However, PD caused by mutations in this gene is rare and very few patients have been reported [3].

Apart from Mendelian forms of inheritance, there are present some common pathogenic pathways for Parkinson's disease. Mutations in GBA gene encoding glucocerebrosidase enzyme is linked with parkinsonism. This enzyme is responsible for partly degradation of alpha synuclein. Mutation causes less production of this enzyme that eventually causes accumulation of alpha synuclein which in turn leads to lysosomal impairment. Increase in alpha synuclein might cause neurotoxicity and PD [1]. Although there are a lot of genetic and environmental factors that are crucial for PD, however no standard diagnostic test present till date that can detect it [3]. Diagnosis of Parkinson's is based on neurological history and symptoms assessment by experienced doctors [2]. By the time that symptoms appear, victims of the disorder have lost 80% or more of their dopamine production capabilities [7].

Treatment of PD is being done via various technologies. Treatment using drugs is mainly aimed to increase the amount of dopamine in brain. Different drugs used for curing are:

Levodopa: It is a non-standard amino acid which reaches to brain from blood and intestine and gets converted into dopamine. It increases the level of dopamine in *substantia nigra* and straitum and relieves the patient for some time. This is one of the major drug in treatment of PD, however significant side-effects of l-Dopa have been reported. It includes nausea, free radical formation causing toxicity, dyskinesia [2].

Levodopa/Carbidopa: L-Dopa is taken in combination with carbidopa to reduce the feeling of nausea. Nausea occurs when levodopa starts getting converted into dopamine inside intestine and blood. Carbidopa prevents it from being converted there and only allows it's conversion inside brain [2].

Dopamine agonists: Two approved dopamine agonists are pramipexole and ropinirole. These mimic the action of dopamine at dopamine receptor. Common side effects are nausea, nightmare and hallucinations [2]. Other than these, many more drugs are being used for PD treatment, but all have major side effects. A successful approach in this field is the use to stem cells to neutralize the loss of dopaminergic neurons and restore dopamine. Different types of stem cells that can be used embryonic stem cells, fetal neural stem cells, adult stem cells and induced pluripotent stem cells (IPSC). The two key approaches for stem cells utilization are exogenous transplantation of stem cells and endogenous stimulation of host brain stem cells to transform into required neuronal cells (the optimal approach for endogenous stem cell-based therapy is unknown). In first method, stem cells are isolated and transplanted into patient's brain. Stems cells divides multiple times and so large number of cells can be obtained that can be genetically modified *in vitro*. Stem cells that are used in this technology are:

Embryonic stem cell (ESC) - These cells are pluripotent and have necessary characteristics required for cell transplantation therapy. ESCs are firstly differentiated into neural precursor cells (NPC) to reduce contamination by proliferative, undifferentiated cells that could form teratomas. These NPCs can divide indefinite number of times and produce dopamine neurons up to 86% purity. Mouse ESCs have shown larger positive results than human ESCs in terms of benefit. But, since mouse ESCs cannot be used for human transplantation and human ESCs are not available all the time, this issue is under concern for clinical applications [4].

Fetal neural stem cells: These stem cells can readily differentiate into dopamine neurons but they have less proliferative capability as compared to embryonic stem cell [4].

Adult stem cell: These stem cells are produced in hippocampus region of the brain and can be developed into dopaminergic neurons. But extracting cells from already damaged brain can be futile and can't be used in routine PD therapy [4].

Induces pluripotent stem cell (IPSC): These cells are produced when mature somatic cells is reprogrammed into immature, embryonic stem cell -like cell by expressing just 4 genes. IPSC had overcame the problems like immune rejection and tissue availability due to being produced from patient's somatic cell [8]. Its results are successful from mouse to human and it efficiently produces fully functional dopaminergic neurons. Though it has lot of advantages, but it might happen that cells isolated from patient have some mutation that can cause more problems instead of producing dopamine. So, tests should be done before applying this technique clinically [4].

Apart from treatments, our daily routine and habits can help us to stay away from PD. Studies showed that caffeine intake, regular exercise and nicotine can reduce the chances of one getting PD. Though cigarette has various adverse effects, but nicotine present in it interacts with receptors to protect dopamine neurons [5]. These are the current approaches of treating Parkinson's disease in present day scenario. Research is being going on in this field to create more techniques for diagnosis and to cure this disease for better future.

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