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A Review of Parkinson's Disease: Diagnosis and Treatment

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Abstract

One of the most frequent neurodegenerative diseases is Parkinson's disease (PD). Recent years have seen notable improvements in the understanding of the disease's pathophysiology in terms of prevalence and incidence. Additionally, there has been a growing understanding that, in addition to the more well acknowledged difficulties, the disorder may also be linked to important causes and disturbances. Despite accumulating suggestive evidence, it has not yet been determined which of the Parkinson's disease treatments possess a neuroprotective effect. There are numerous therapy options available, but there is no known cure for Parkinson's disease. As the illness worsens, additional treatments are available, but managing the symptoms of PD is still difficult and will benefit from more clinical study.

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INTRODUCTION

One of the most prevalent chronic neurodegenerative diseases affecting older persons is Parkinson's disease (PD). Although patient's main concern is movement disability, pulmonary issues are to blame for the majority of fatalities [1]. Previous investigations have shown that people with PD had impaired lung function. Reduced respiratory muscle strength and thoracic stiffness have been linked to obstructive, restrictive, and mixed forms of respiratory dysfunction. The majority of research discuss pulmonary dysfunctions in patients with intermediate and advanced disease states, where physical decline is noticeable. Since physical deterioration and changes brought on by ageing are the main contributors to pulmonary dysfunction in older people. The neurological symptoms of the illness are brought on by the degeneration of nerve cells in the substantia nigra, a region of the midbrain that supplies the basal ganglia with dopamine. It is assumed that the protein alpha-synuclein accumulates into Lewy bodies inside the neurons and is the reason for this cell death [2]. The basic neurological symptoms are collectively referred to as Parkinsonism or Parkinsonian Syndrome.

Disease Prevalence and Incidence

Parkinson's disease (PD) is a neurological, progressive disease that impairs motor skills and often affects people over the age of 50. Estimated prevalence rates for diagnosed PD in households were 0.2% and 4.9%, respectively, according to survey data collected in Canada from 2010 to 2012. In Canada, it was projected that there were 55,000 persons living in households and 12,500 of them were in long-term care facilities. In the household population and long-term care facilities, specifically, 79% and 97% of persons with a PD diagnosis were at least 65 years old. The incidence and severity of PD

both rise with age, and 85% of identified cases occur in adults over 65, demonstrating that PD is predisposed to ageing. Males and Caucasians are more likely to have PD than other races [3].

Resting tremors, stiffness, bradykinesia, and postural instability are hallmarks of Parkinson's disease (PD), which results in loss of control over voluntary movement. By 10 to 15 years after the commencement, the disabling disability may have worsened the motor function deficit. The persistent loss of dopaminergic neurons in the nigrostriatal area of the brain and dopamine depletion are the underlying causes of motor symptoms. Along with nonmotor symptoms like gastrointestinal issues, neuropsychiatric symptoms, sleep issues, urine problems, discomfort, and issues with impulse control, PD is also linked to these [4].

Dyskinesia and motor fluctuations, which can appear as unpredictable "off" moments (immobility/hypomobility), unpredictable "on/off" fluctuations, and "end-of-dose wearing off" episodes, are common in patients with advanced-stage PD. Rigidity, dystonia, tremors, and freezing can all occur during "off" periods, in addition to difficulties breathing and eating. As the condition advances, patients typically report that their daily "off" time increases while their "on" time decreases [5].

Standards of Therapy

The severity of the symptoms and the disease, as well as the characteristics of the patients, influence the treatment options for idiopathic PD. Pharmacologic and surgical therapy are the two primary categories under which motor symptom treatments fall. Based on their mode of action, pharmacologic treatments can be further subdivided into neuroprotective and symptomatic therapy. In actual practice, the majority of PD treatments are pharmaceutical, taken orally, and focused on treating both the motor symptoms of PD and the underlying cause of declining dopamine levels within the brain [6].

There are several dopaminergic anti-PD drugs available in different countries. Levodopa, a dopamine precursor, is the first-line treatment for Parkinson's disease (PD) because it is successful in reducing neurological signs like tremor, rigidity, and bradykinesia by correcting dopamine insufficiency in the nigrostriatal area of the brain.

Dopamine receptor agonists, which are assumed to stimulate post-synaptic dopamine receptors and are second-line treatments due to their variable efficiency, are another type of dopaminergic medication used to treat neurological signs [7].

Levodopa is effective for the majority of PD patients, however after three to five years of treatment, 20% to 75% of PD patients have motor problems, which can last for up to 50% of the waking day. In more severe cases, the controlled-release formulation of levodopa/carbidopa is frequently used to control motor fluctuations and "wearing off" episodes; nevertheless, the propensity for irregular absorption and a delayed response makes this treatment ineffective. Levodopa can be used with other medications to cut down on "off" time. Rasagiline and selegiline are monoamine oxidase type B inhibitors, which stop the brain's dopamine metabolism. Entacapone is one catechol-O-methyltransferase inhibitor that boosts levodopa's peripheral bioavailability. Trihexyphenidyl and benztropine are two examples of anticholinergics; their usage in older individuals is constrained due to ineffectiveness and neuropsychiatric adverse effects [8].

Pathology, Aetiology and Pathogenesis

Cell loss in the substantia nigra, particularly in the ventral section of the pars compacta, is the major sign of Parkinson's disease. When compared to the same region in those who are not affected, this part of the brain has lost 50-70% of its neurons at the time of death. The medulla oblongata/pontine tegmentum as well as the olfactory bulb have shown the first pathogenic abnormalities in Parkinson's disease (PD). Patients are in Braak stages 1 and 2 at this early time. The substantia nigra, parts of the midbrain, and the basal forebrain are affected as the disease progresses to Braak stages 3 and 4. Its pathogenic alterations manifest themselves within the neocortex [Figures 1 and 2] [9].

Causes

Although there is no established aetiology for Parkinson's disease, several factors seem to be involved, such as:

1. Genes: The cause of Parkinsonian is associated with a few specific genetic abnormalities, according to researchers. These, however, are uncommon Perhaps several members of the family also suffer from Parkinson's condition.
2. Each of these genetic indicators has a relatively modest risk of Parkinson's disease, even though some gene alterations may seem to enhance the incidence of the illness.
3. Environmental triggers: There is a slight chance that later-onset Parkinson's disease will be brought on by exposure to specific poisons or environmental factors [10, 11].

Researchers have also discovered that people with

Table 1: PDS Brain Bank Criteria for the diagnosis of PD

Steps
Step 1: Diagnosis of a parkinsonian Syndrome
One of the following as well as bradykinesia
· Muscular rigidity
· Rest tremor (4–6 Hz)
· Postural instability unrelated to main cerebellar, proprioceptive, ocular, or even vestibular impairment.
Step 2: Parkinsonian disease (PD) exclusion criteria
History of:
· Step-by-step progression with repeated strokes
· Consistent head trauma
· Drugs that deplete dopamine or antipsychotics
· Definite encephalitis and/or ocular crises unresponsive to medication
· Multiple affected relatives
· Persistent remission
· Negative reaction to high levodopa dosages (assuming malabsorption is not present)
· After 3 years, strictly unilateral characteristics
· After three years, the traits are strictly unilateral.
· Additional neurological characteristics include early severe dementia with language, memory, or praxis difficulties, supranuclear gaze palsy, cerebellar symptoms, early severe autonomic involvement, Babinski sign, as well as cerebellar signs.
· Neuroimaging evidence of a brain tumour or communicating hydrocephalus.
· Exposure to a recognised neurotoxin.
Step 3: Parkinsonian Disease (PD) Supportive Criteria
For a definite PD diagnosis, three or more are necessary:
· Unilateral onset
· Rest tremor present
· Progressive disorder
· Onset side is most affected by persistent asymmetry
· Excellent reaction to levodopa
· Severe chorea brought on by levodopa
· Response to levodopa for more than 5 years
· Over ten years of clinical experience

Table 2: Typical reasons for tremor

Tremors
Rest Tremor
· Parkinson's Disease
Postural and Action Tremor
· Hyperthyroidism
· Exaggerated physiological tremor
· Essential tremor
· Substance-induced (ex., -agonists)
· Dystonic trembling
Intention Tremor
· Cerebellar abnormalities

Table 3: Differentiating causes of Parkinsonism

S.No	Condition	History	Clinical Features	Investigation	Management
1.	Drugs that cause Parkinsonism	Prior drug use, primarily neuroleptic medication and antiemetics	May be connected to oromandibular dystonia as well as akathisia	Considering history	Stop using the offending drug. Anticholinergic medications could be beneficial for tremor
2.	Multisystem atrophy	Parkinsonism or shaky gait, whether or not there is autonomic dysfunction	Orthostatic hypotension, no tremor, symmetrical symptoms, cerebellar characteristics, erectile dysfunction, and a subpar response to levodopa	Sphincter EMG, MRI of the brain	Trials of levodopa and amantidine as well as fludrocortisone are used to treat postural hypotension.
3.	Progressive supranuclear palsy	Early regresses, changes in cognition or behaviour	Poor response to levodopa, gaze palsy (downward rather than upward), axial rigidity, frontal as well as pyramidal symptoms	MRI brain	Levodopa trial
4.	Normal-pressure hydrocephalus	Cognitive impairment, ataxia, as well as incontinence of the bladder	Dementia with a festering gait	Therapeutic lumbar puncture, brain CT or MRI	Check for a ventriculoperitoneal shunt
5.	Dementia with Lewy bodies	Preceding or coexisting with parkinsonism is dementia	Imaginal delusions	Psychometry as well as brain MRI	Consider cholinesterase inhibitor

Parkinson's disease have a variety of brain abnormalities, although it is unclear why these changes take place. One of these modifications is the occurrence of Lewy bodies. One of the microscopic signs of Parkinson's disease is the presence of clusters of certain chemicals within brain cells. Because of what they are, Lewy bodies are thought to be crucial to analysing the mechanisms leading to Parkinson's disease.

The presence of alpha-synuclein in Lewy bodies. Alpha-synuclein, often known as a-synuclein, is a naturally occurring protein that is present in large amounts and is thought to play a key role in Lewy bodies. It is clumped as well as found in all Lewy bodies; cells cannot break it down. People who eventually acquire Parkinson's disease have clumped alpha-synuclein protein in their spinal fluid, according to research.

Diagnosis

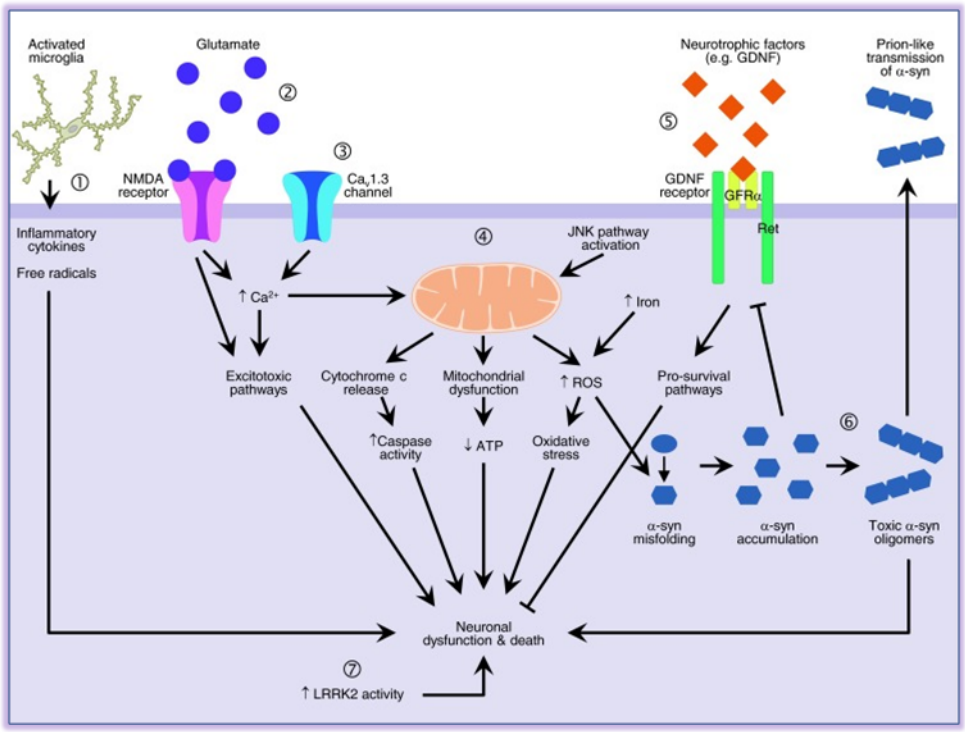

Figure 1: Targeted Neuroprotective Therapies in Parkinson's Disease (PD)

There are many signs and symptoms of Parkinson's disease, however, these are the most common diagnostic signs [12]:

1. Sluggishness and lack of mobility
2. Stiffness
3. Shaking.

Parkinson's disease physical symptoms involve:

1. Bradykinesia, or slowing of movement
2. Lack of movement (hypokinesia), including loss of facial expression, difficulties with fine movements, and loss of arm swing
3. Rigidity
4. Rest tremor.

Normally unilateral at diagnosis, these symptoms become bilateral as the condition worsens. Additional symptoms such as postural instability (such as a propensity to sag backwards after a forceful tug from the examiner, or the "pull test"), cognitive impairment, as well as orthostatic hypotension (OH) may appear later in the disease's progression.

Parkinson's disease is sometimes said to be idiopathic Parkinson's disease. To distinguish Parkinson's disease from other Parkinsonian causes such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA), cannot be accurately described singly.

Lewy bodies as well as catecholaminergic neuronal degeneration are the pathological hallmarks of Parkinson's disease, according to standard definitions. For a variety of reasons, utilising such a pathological definition of Parkinson's disease was difficult, such as [13]:

1. In real life, a pathology diagnosis is not useful.
2. People without any outward signs of Parkinson's disease have lewy body inclusions in catecholaminergic neurones; it is assumed that these cases are preliminary.
3. Despite the possibility that Lewy bodies have not been observed in otherwise healthy patients with Parkinson's disease who had Parkin mutations, these unusual young-onset genetic examples of the illness are unrelated to idiopathic Parkinson's disorder.

The identification of monogenic types of Parkinson's disease in recent years has made the initiative to genetically classify the condition feasible. Such families make up a relatively small percentage of cases, nevertheless.

The way a patient reacts to dopaminergic treatment is another potential indicator of Parkinson's disease.

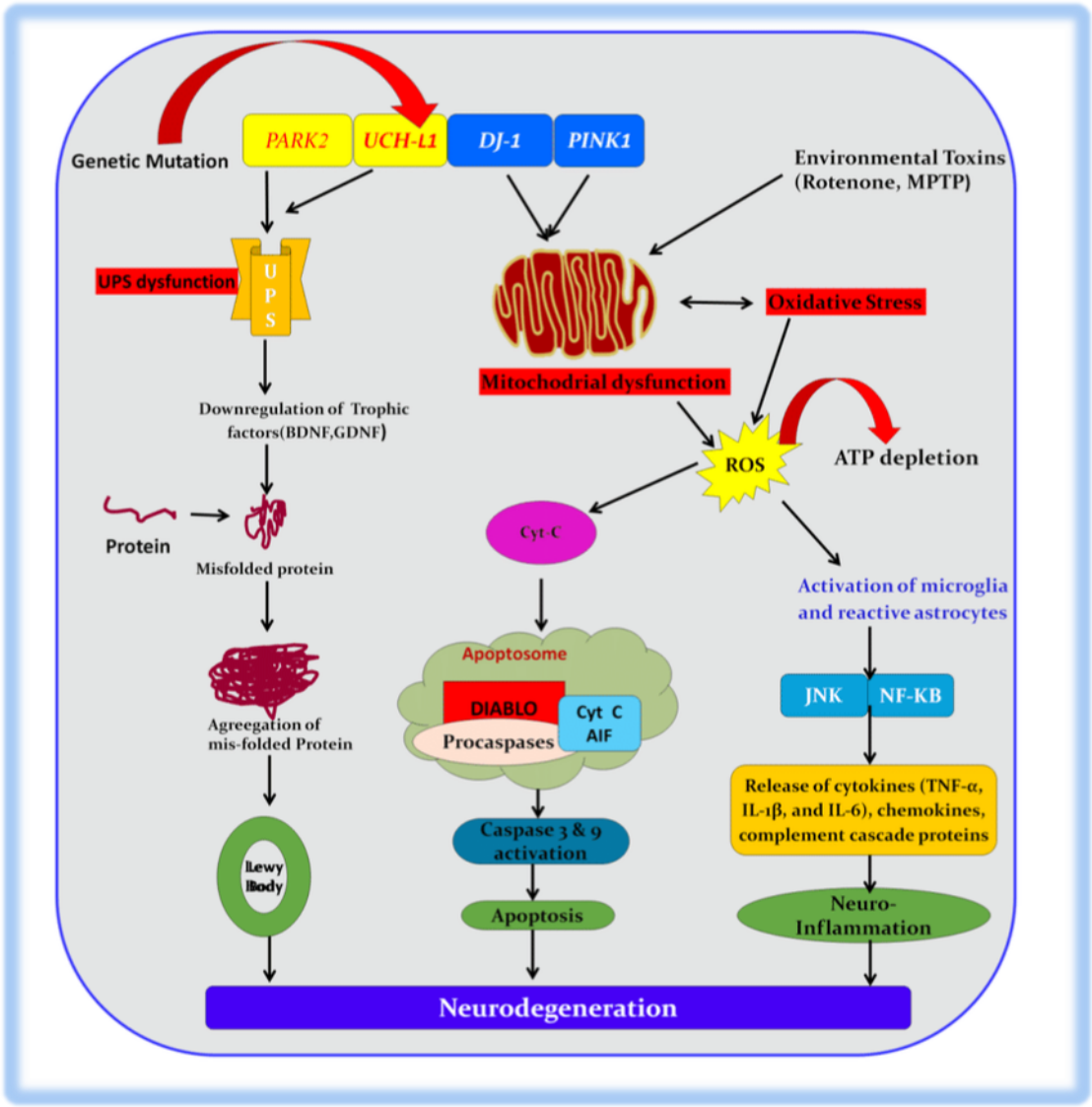

Figure 2: Pathophysiology of Parkinson's Disease

However, disorders other than Parkinson's disease, such MSA, can also exhibit similar dopaminergic reactivity.

Parkinson's disease has also been suggested to be defined by the loss of dopaminergic neurons shown on radioactive Single photon emission computed tomography (SPECT) or positron emission tomography (PET). Unfortunately, disorders like MSA and PSP, which are not associated with Parkinson's disease, also exhibit this decrease.

Given these challenges, it is generally agreed that a clinical diagnosis of Parkinson's disease should be used. The PDS Brain Bank Criteria [Table 1], which were developed, are the clinical indicators for Parkinson's disease diagnosis that are the most extensively used [14].

The prognosis of a person with probable Parkinson's disease depends significantly on the accuracy of the diagnosis. Parkinson's patients will live longer and respond more favourably to dopaminergic therapy than those with MSA or PSP.

Additionally, other illnesses that show with tremor must be distinguished from Parkinson's disease. This can be particularly challenging because Parkinson's disease can manifest as an essential tremor-like postural and movement tremor [Table 2].

Additionally, alternative causes of Parkinsonian syndrome or parkinsonism must be distinguished from Parkinson's disease [Table 3]. Multiple cerebral infarctions and degenerative parkinsonian disorders like MSA and PSP are the most common causes of issues. Since extrapyramidal symptoms and indications are frequent in elderly adults, differential diagnosis can be challenging [15].

Management of Parkinson's Disease

Once a clinical diagnosis has been made, it is critical to take the time to fully explain the condition and its ramifications to the patient and their family. Some patients might require some additional time to accept and adjust to the diagnosis. Connecting patients with PD nurse specialists and PD charitable organisations, if any are accessible locally, can be very helpful. Deciding to start Parkinson's disease (PD) medication can be difficult, especially within the very early stages of such a disorder whether there may not be much functional loss. The decision that should be taken by involving the patient's active involvement was determined according to the severity of physical impairment in comparison to the potential adverse effects of pharmacological therapy. Growing in significance is the question of whether neuroprotection is a possibility with early treatment. This question has not yet been resolved despite numerous in vitro, in vivo, as well as human research, A large portion of the latter use PET or SPECT imaging as substitute indicators of nigrostriatal dopaminergic activity. Therefore, there are currently just symptomatic treatments available and no known neuroprotective therapy. Early on in the course of treatment, the objective is to lessen symptoms as well as enable complete independence and normal function for the patient. The drug must be well tolerated to work. Monotherapy is often preferred as a result. Treatment is deemed successful if patients can continue getting it with few side effects, a satisfying decrease in symptoms, as well as a sense of well-being that enables them to live freely and productively [16].

Treatment of Parkinson's Disease

First-line levodopa treatment

Long-term levodopa medication frequently generates impairing side effects. After starting levodopa, dyskinesias caused by the drug typically appear at a rate of 10% each year, while this rate is higher in patients with younger onset. While dyskinesias are mostly connected to the length of levodopa treatment, motor fluctuations are most strongly correlated with the severity of the disease and the dose of levodopa exposure. Intermittent activation of dopamine receptors appears to be linked to the emergence of drug-induced dyskinesias in Parkinson's disease (PD). Levodopa has a short half-life of 60 to 90 minutes, and its pulsatile delivery to a denervated striatum appears to be a significant aetiological element. Additionally, unfavourable effects manifest more quickly the more severe the nigral neuronal loss was before to levodopa injection. The potential neurotoxicity of levodopa has been a contentious topic. In a sizable, randomised, placebo-controlled clinical investigation involving patients with early PD who had not previously received symptomatic therapy, the ELLDOPA study attempted to address the issue. The study's objective was to determine whether levodopa medication had an impact on how quickly the condition developed. After a 2-week washout period, patients who received all three levodopa doses performed better on the UPDRS than the placebo group as a whole, in a dose-responsive pattern. This would suggest a neuroprotective effect, but it's also possible that the 2-week washout period wasn't long enough. Levodopa's potential for either neurotoxicity or neuroprotection is still up for debate. However, utilising tiny doses of levodopa that are individualised for the patient's needs is preferred due to the danger of motor problems over time that are dose-dependent [17].

First-line dopamine agonist treatment

In the market, there are six oral dopamine agonists. Ergot substances include bromocriptine, pergolide, cabergoline, as well as lisuride. Pramipexole along with ropinirole are ergot-free drugs. Rotigotine, a non-ergot agonist, is available as a transdermal patch. These medications all work by turning on post-synaptic dopamine receptors. Patients with advanced PD who were also on levodopa were the first group of patients for whom the dopamine agonists were approved. They were first-line treatments because they were effective in easing motor symptoms and could delay the administration of levodopa and the inevitable onset of levodopa issues. In monotherapy investigations, levodopa as well as dopamine agonists have been contrasted. In comparison to levodopa, studies of the more recently developed dopamine agonists revealed a significantly lower rate of motor problems in patients starting agonist monotherapy. Levodopa and pramipexole groups experienced the same quality of life (QoL) outcome measures during the four-year CALM-PD research. Confusion and hallucinations are more likely with dopamine agonist therapy than with levodopa therapy alone, and the adverse effect profile is comparable to that of levodopa. The difficulty of first-line treatment for PD is that dopamine agonists lead to fewer motor symptoms and the same QoL ratings but at the expense of a higher incidence of side effects as well as lower efficacy as determined by the UPDRS. Contrary to the prevalent belief, patients over the age of 75 can tolerate dopa agonist monotherapy without experiencing adverse effects as frequently as younger patients. Studies with the newer agonists have disproved this claim. However, as mentioned above, utilising agonists in the elderly calls

for further caution. Selecting a dopamine agonist is frequently a decision based on empirical evidence. There hasn't been much research comparing the agonists head to head. However, ergot agonists, particularly cabergoline as well as pergolide, have been linked to an increase in reports of non-inflammatory fibrotic degeneration of heart valves, and as a result, they are no longer advised as first-line therapies. For patients who continue using ergot-derived agonists, regular monitoring is advised, including ESR, chest X-rays, and 6-monthly echocardiograms. The non-ergot-derived dopamine agonists ropinirole, pramipexole, as well as rotigotine, are frequently utilised. An elevated risk of developing pathological gambling is a rare but significant side effect of pramipexole that has been documented the most frequently to date [18].

First-line MAO-B inhibitors

Following the DATATOP trial, MAO-B inhibitors were widely used due to their demonstrated effectiveness in alleviating symptoms and purported "neuroprotective" impact. A later study by The United Kingdom Parkinson's Disease Research Trial Group, which included over 700 patients with moderate early PD, seemed to indicate, however, that selegiline and levodopa treatment appeared to significantly increase mortality when compared to levodopa alone or bromocriptine treatment alone. Further research that suggested the contrary, a potential decline in mortality, did not confirm this finding. MAO-B drugs lower disability, the requirement for levodopa, and the prevalence of motor fluctuations without having significant adverse effects or raising mortality, according to a more recent meta-analysis of 17 randomised studies including a total of 3525 individuals. However, first-line monotherapy with MAO-B inhibitors may be useful for PD patients. Studies using the new MAO-B inhibitor rasagiline have shown its effectiveness in both early and advanced illness. Similar to the dopamine agonist trials mentioned above, more research is required to confirm the results of the TEMPO wash-in trial, which are consistent with a disease-modifying impact [19].

The role of surgery in PD

For over 50 years, surgery has been utilised to treat PD. Patients, particularly those with severe tremors, were occasionally referred for ablative surgery from the beginning of the 1950s. This procedure was normally carried out on the thalamus upon the opposite side. Following the invention of levodopa, surgical intervention lost favour. Ironically, medical experts are now rethinking surgical intervention because of the growing awareness of levodopa-related issues. Lesion surgery, often in the form of pallidotomy, was once the main emphasis since it was beneficial, especially for dyskinesias brought on by levodopa. Bilateral subthalamic stimulation is the treatment most frequently used to lessen bradykinesia, tremor, and rigidity as well as to lessen drug-related motor problems. This has the potential to be highly advantageous. Despite the operation's technical difficulty, unfavourable occurrences are unlikely in skilled hands. The availability of this type of treatment is however restricted by the infrastructure and support staff needed to evaluate, perform, and monitor patients. Concern has also been raised concerning the rise in psychiatric side effects, particularly depression after DBS. Because of this, patients who have cognitive impairment or major depression are not appropriate candidates for this type of therapy. The majority of STN DBS procedures are conducted on individuals under the age of 75 who do not have any substantial systemic co-morbidities and who have no evident structural abnormalities on MR imaging. Patients who are dependent on levodopa and independent of it should be levodopa-responsive [20]. Most patients will have had their condition for at least 5 years before other atypical parkinsonism causes can be identified. When Vim DBS is used to treat debilitating tremors, age seems to be less important. DBS of the pedunculopontine nucleus may help to enhance axial stability, according to recent studies. When evaluating a patient for DBS, a skilled multidisciplinary team is required.

CONCLUSION

One of the most frequent neurodegenerative diseases is Parkinson's disease (PD). The development of abnormal protein aggregation, which leads to cell dysfunction and ultimately cell death, within particular populations of neurons is thought to be significantly influenced by a mix of genetic as well as environmental factors. To rule out any further causes of Parkinson's disease, a high level of suspicion should be maintained while the diagnosis is still clinical. There are numerous medicines along with surgical techniques available today to treat both early as well as late-stage consequences of PD. The diagnosis and treatment of PD are receiving more and more attention. It is envisaged that future studies in Parkinson's disorder will focus on the concept of disease-modifying drugs that offer neurological protection.

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