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A New Era for the Treatment of the Parkinson disease

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ABSTRACT:The parkinson is a disease in which there is imbalance between dopamine and acetylcholine level. It is chronic progressive neurodegenerative disorder like movement problems such as rigidity, slowness, and tremor. More than 6 million individuals worldwide have Parkinson disease. Risk factors include age, male gender and some environmental factors. Parkinson disease is the second-most common neurodegenerative disorder that affects 2–3% of the population≥ 65 years of age. Neuronal loss in the substantia nigra, which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of α-synuclein are the neuropathological hallmarks of Parkinson disease. Multiple other cell types throughout the central and peripheral autonomic nervous system are also involved, probably from early disease onwards. In this review we will provide overall information of disease and Novel drug delivery systems to treat Parkinson disease. Since PD is not cure but there are lots of new technologies in future like deep Brain Stimulation, Stem cell therapy, Biomarkers which help in the treatment of PD.

KEYWORDS: Parkinson Disease , Cells , Neuron, Dopamine , Acetylcholine

I. INTRODUCTION

Bradykinesia (bradykinesia), stiffness, postural instability, and tremor are all symptoms of Parkinson's disease (PD). neurodegeneration with Lewy bodies—neuronal inclusions made of -synuclein—is thought to be the classic pathologic correlate of Parkinson's disease (PD)[1].Even though tremor at rest, bradykinesia, increased tone, and loss of postural reflexes are recognised as the cardinal signs of Parkinson's disease, making the diagnosis can be difficult. The treatment and prognosis for idiopathic Parkinson's disease must be separated from those for other types of parkinsonism[2].

James Parkinson initially described Parkinson's disease (PD) in 1817. It is a progressive degenerative ailment that primarily affects older persons. Degeneration of neurons in the substantia nigra pars compacta (SN-PC) and the nigrostriatal (dopaminergic) tract is the most common lesion in Parkinson's disease (PD). As a result of lack of dopamine (DA), which regulates muscle tone and coordinates movement, in the striatum. The motor dysfunction results from an imbalance between the dopaminergic (inhibitory) and cholinergic (excitatory) systems in the striatum. Even if the cholinergic system is not directly affected, its inhibition (by anticholinergics) often leads to a return to equilibrium[3].Although the exact cause of the nigrostriatal neurones' selective degeneration is unknown, it appears to be complex. oxidative free radical production, ageing, genetic susceptibility, N-methyl-4-phenyl tetrahydropyridine Environmental poisons that resemble (MPTP) and excitotoxic neuronal death brought on by Ca2+ overload mediated by NMDA-receptors (excitatory glutamate receptors) have all been implicated. Neuroleptics, such as metoclopramide (a dopaminergic blocker), are currently very prevalent causes of drug-induced reversible parkinsonism, although reserpine (a DA depleter) is a historical cause[3].

II. SYMPTOMS

1).The motor symptoms of the Parkinson disease:- Before the cardinal motor characteristics of Parkinson's disease (PD) begin to manifest, it is thought that up to 80% of the dopaminergic cells in the nigro-striatal pathway are destroyed. The disease can typically be identified by its initial motor signs. An additional symptom, such as muscle rigidity, resting tremor, or postural instability, is required for the diagnosis of bradykinesia, which is characterised by a slowness of start of voluntary movements and a progressive reduction in speed and amplitude of repeating motions. he diagnosis involves determining at least three supportive criteria for Parkinson's disease (PD), such as unilateral onset of symptoms, persistent asymmetry of clinical symptoms, a good response to levodopa treatment, and induction of dyskinesias by pharmacological means. The diagnosis involves excluding symptoms that might

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indicate other aetiologies, such as parkinsonian syndromes that have their own neuropathological changes[54].

2).The non motor symptoms of the Parkinson disease:-Patients may have a range of pre-motorsymptoms prior to the onset of motor symptoms and the establishment of the diagnosis. Symptoms may appear up to ten years or more before the diagnosis, and the presence of non-motor symptoms may cause the diagnosis to be delayed. According to one research of 109 newly diagnosed patients who had not yet begun therapy, symptoms like apathy, excessive daytime sleepiness, sleep issues, and constipation may occur in up to 60–70% of patients before the diagnosis and were more prevalent than in healthy controls. Additional pre-motor symptoms were memory issues, loss of smell and taste, mood swings, increased perspiration, exhaustion, and discomfort. The seeds of Mucuna pruriens L. (DC), which have a long history of safe usage in the disease, are a naturally occurring source of levodopa that is recommended by Ayurveda. Its pharmacokinetic profile is different from synthetic levodopa, according to clinical trials, and thus is anticipated to lessen any unwanted motor problems. Furthermore, its seed extracts have demonstrated neuroprotective advantages unrelated to levodopa., the inability to appreciate activities typically regarded enjoyable, was another pre-motor sign. indigestion and dream-like behaviour[4].

3).Neuropsychiatric symptoms:-Even in the early stages of Parkinson's disease, neuropsychiatric symptoms are prevalent, have a significant impact on daily functioning and quality of life, increase the burden of caregiving, and raise the chance of nursing home admission. Many neuropsychiatric symptoms, in addition to cognitive impairment, have been observed[5]. Even in the early stages of Parkinson's disease, neuropsychiatric symptoms are prevalent, have a significant impact on daily functioning and quality of life, increase the burden of caregiving, and raise the chance of nursing home admission. Many neuropsychiatric symptoms, in addition to cognitive impairment, have been observed. Visual hallucinations and illusions are frequent in Parkinson's disease (PD) and are said to affect 30% to 40% of patients. Visual hallucinations have also been documented to happen before receiving medical treatment, despite the fact that practically all antiparkinsonian medicines have been reported to cause hallucinations and psychosis. The illness process appears to be responsible for neuropathological alterations in the hippocampus and amygdala that are related to the aetiology. Anxiety and depression are two additional prevalent PD symptoms[5 6].

III. ETIOLOGY

Although environmental and genetic variables have long been suspected to have a role in the aetiology of Parkinson's disease (PD), there has never been concrete proof to support either theory. Six distinct genes, nevertheless, have only been linked to familial PD in the last 8 years. They all concur in favour of the idea that shared pathogenesis processes exist throughout the range of PD aetiologies. With a Mendelian pattern of inheritance, PD is specifically brought on by mutations in -synuclein, parkin, UCHL1, DJ1, PINK1, and LRRK2. Since -synuclein and parkin are mitochondrial proteins, DJ1 and PINK1 overexpression results in mitochondrial abnormalities. The operation of the proteasomal system is impacted by the same proteins that are involved in the response to oxidative stress. Neurologic illness is influenced by heavy metals, including iron and manganese. The majority of the time, these illnesses are linked to abnormal environmental exposures or abnormal bodily accumulations of heavy metals. There is growing understanding that naturally occurring heavy metals in the body may contribute to the aetiology of disease by causing the creation of free radicals. Movements become erratic when the basal ganglia, a region of the brain, are impacted. One of the most prevalent movement diseases, Parkinson's disease is linked to the death of neurons in the basal ganglia's substantia nigra pars compacta (SNpc). Dopamine and elevated iron concentrations together may be a factor in the SNpc's particular susceptibility to injury. The auto-oxidation of dopamine can result in free. Environmental influences, however, have not been well-characterized. The poisons that have been shown to be able to kill nigrostriatal cells, however, seem to work together by interfering with mitochondrial activity, causing oxidative stress, and altering proteasomal activity. As a result, common motifs in the etiopathogenesis of PD are starting to emerge[7].

Non genetic causes of the Parkinson disease:-

I. The 1980s discovery of a cluster of parkinsonism caused by the neurotoxic pyridine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) stimulated research into the monogenetic origins of Parkinson's

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disease (PD). Epidemiologic studies since then have revealed risk variables, albeit their findings do not prove causation. Several studies have linked increased risk to pesticide exposure. The risk of living in the country and some jobs is also mentioned. Non-steroidal anti-inflammatory medicines (NSAIDs), cigarette smoking, and caffeine usage all tend to reduce the risk of Parkinson's disease (PD), whereas dietary fat and milk consumption, excessive calorie intake, and head trauma may raise the risk. The underlying causes of PD are probably complex. Combinations of risk and protective variables as well as underlying genetic predisposition are likely all involved.

IV. PATHOGENESIS

The substantia nigra and other specific brain regions in Parkinson's disease usually include the characteristic neuronal inclusion known as the Lewy body. Everywhere there is an excessive loss of neurons, it manifests itself primarily as structurally altered neurofilament. It happens in certain elderly people and infrequently in other central nervous system degenerative illnesses. The age-specific prevalence of Lewy bodies increased from 3.8% to 12.8% in 273 brains of people dying from diseases other than Parkinson's disease between the sixth and ninth centuries. These accidental Lewy body disease instances may be presymptomatic Parkinson's disease cases, according to associated pathological findings, which emphasises the significance of age (time) in the progression of the illness. Given the frequent and extensive[9].

NOVEL TECHNIQUES TO TREAT PARKINSON DISEASE

1) Deep Brain Stimulation
2) Neural Transplantation
3) Biomarkers
4) Neuroprotective Therapy
5) Gene Therapy
6) Stem cells therapy
7) Ayurveda
8) Designer Neuron

1)Deep Brain Stimulation :-

The pallidum and the subthalamic nucleus have now been treated with deep brain stimulation at high frequency, which was initially utilised in 1997 to substitute thalamotomy in treating the recognisable tremor of Parkinson's disease. A crucial node in the basal ganglia's functional control of motor activity is the subthalamic nucleus[10].DBS is becoming more widely regarded as an additional treatment for Parkinson's disease (PD). For patients with intractable tremor or those who experience long-term side effects of levodopa medication such motor fluctuations and severe dyskinesias, it is regarded as a surgical treatment alternative. Contralateral tremor is significantly reduced by thalamic stimulation of the ventral intermediate nucleus (Vim), while other Parkinson's disease symptoms are unaffected. For the treatment Source of figure of advanced Parkinson's disease, the subthalamic nucleus (STN) and the internal section of the globus pallidus (GPi) are targeted[11].In order to intervene and lessen the impact of abnormal brain signals in illness situations, brain-computer interfaces (BCIs) may be used. Here, we demonstrate the viability of this strategy by interpreting pathogenic brain activity in patients with advanced Parkinson disease (PD) using a BCI, and then using this input to regulate the timing of therapeutic deep brain stimulation (DBS). Our objective was to show that real-time personalization and optimisation of stimulation might outperform traditional continuous DBS in terms of effectiveness and efficiency[12].Deep brain stimulation (DBS) is effective for treating Parkinson disease (PD) for up to 1 or 2 years, however there are few long-term outcome data available. We examine the clinical implications of the evidence on the long-term effects of DBS in this Review. The evidence suggests that subthalamic nucleus DBS improves motor function for up to 10 years, however the degree of improvement tends to diminish over time. This is true even if many patients are lost to follow-up. Functional scores recorded when taking medicine worsen more quickly than functional scores recorded when not taking medication, which is consistent with the decline of non-dopaminergic pathways[13].

2) Neural Transplantation:-

Forum Neural transplantation in putaminal 18F-dopa uptake has also been very variable, which implies that variations in the grafted dopaminergic neurons' survival and growth may play a significant role in the patients' recovery[14].A successful experimental treatment for CNS illness, particularly Parkinson's disease, is neural transplantation[15].The fetal nigral implants have given PD patients a slight improvement in their motor function. This is in line with positron emission tomography results showing the presence of

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small surviving grafts (PET)[16]. The expression of dopamine transporters (DATs) and mitochondrial morphology were studied in human foetal midbrain cellular transplants in order to ascertain the long term health and function of transplanted dopamine neurons in Parkinson's disease (PD) patients. For at least 14 years following transplantation, DAT was strongly expressed in the putamen and caudate of the transplanted dopamine neuron terminals in the reinnervated host. At all time points, the transplanted dopamine neurons displayed a sound and non-atrophied morphology[17].There is a critical unmet need for Parkinson's disease (PD) medicines that alter the course of the disease rather than only treating symptoms. One method to accomplish this is to use brain transplantation to restore the dopaminergic nigrostriatal system, which is deteriorating. Patients who received cell transplants made from foetal ventral mesencephalon cells initially experienced positive effects, according to a number of small, independent open-label studies[18].

3)Biomarkers:-

Last but not least, the Exposome concept is novel in the field of biomarker discovery and is proposed as a technique to advance the finding of biomarkers for neurological illnesses. Exposome-wide association studies (EWAS) are used in the first step of the two-stage plan to profile omic characteristics in serum and find molecular biomarkers. The second phase entails using this knowledge base in subsequent studies. This approach is distinctive in that it advocates a shift away from utilising exclusively reductionist tactics to find biomarkers of exposure and disease and towards the use of data-driven (omic) strategies in examining diseased and healthy populations. 1) Developments in our comprehension of the molecular pathways causing PD that have resulted in possible biomarkers[19].Biomarkers, or traits that can be assessed as indicators of a typical biological process, are particularly important in the context of Parkinson's disease. Given the location of pathology and how the resulting clinical phenotype changes over time, Parkinson's disease is a chronic neurodegenerative disorder that is challenging to investigate. The hope for the clinician is that biomarkers will aid in the diagnosis of symptomatic and presymptomatic disease or provide surrogate end points to demonstrate clinical efficacy of new treatments, such as neuroprotective therapies, and help stratify this heterogeneous disease. Currently, we lack a definitive diagnostic test. As no biomarker is likely to serve all of these purposes, we must understand how each has been validated in order to comprehend their applications and restrictions[20].

Classification of biomarkers

Generally speaking, there are two main categories of PD biomarkers: I premotor (preclinical) biomarkers, and (ii) motor (clinical) biomarkers. These biomarkers can also be separated into two groups: in vivo biomarkers and in vitro biomarkers. We have now classified these indicators into the following categories: (a) clinical (b) biochemical (c) biophysical (d) physiological € genetic (f) morphological (g) immunological

Nonmotor (premotor/preclinical) biomarkers:-

The possibility of a protracted preclinical or asymptomatic phase in PD is now well acknowledged. Hence, a lengthy prodromal phase is compatible with the presence of early risk factors for PD. As previously mentioned, significant substantia nigra degeneration and striatal dopamine loss take place prior to the onset of clinical symptoms. Moreover Lewy bodies, the histological sign of Parkinson's disease, can develop in as few as 10% of healthy people over the age of 50.

Presymptomatic biomarker, Clinical biomarkers, Sex hormones, Molecular pathology biomarkers, Serotonin as a biomarker of PD, Nonmotor biomarkers, Sleep disturbance, Electrophysiological biomarkers, Lewy bodies, CSF biomarkers, Advanced end glycation products (AGE), Genetic biomarkers, Omics biomarkers, In vivo molecular imaging biomarkers, Cytokines as biomarkers, Neuroinflammatory biomarkers, Multimodality biomarkers, Pharmacological biomarkers, Molecular biomarkers in drug development[21].

4)Neuroprotective therapy :-

Levodopa's release in the late 1960s marked a turning point in the treatment of Parkinson's disease (PD). Unfortunately, a significant drawback to this otherwise successful treatment is the emergence of motor problems with long-term levodopa administration. The primary goal of clinical studies over the past few decades has been to improve the medical and surgical management of these problems. Basic research has also concentrated on developing our knowledge of the mechanisms underlying motor difficulties and developing strategies for avoiding them. Neuroprotective tactics may be crucial in

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preventing the onset and lessening the severity of levodopa-related adverse effects by delaying the need for levodopa therapy by slowing or stopping the progression of the disease[22].

5)Gene therapy:-

Dopamine replacement medication is currently the predominant treatment for Parkinson's disease (PD), although it comes with a number of adverse effects and doesn't stop the disease from progressing. A potential way to enhance current therapy is provided by the science of gene therapy. For PD gene therapy, both non-disease and disease-modifying transgenes have been examined in both animal and human investigations. In randomised clinical studies, non-disease modifying therapies that target dopamine or GABA production have shown effective and promising in alleviating PD symptoms; however, further research is required before these therapies may be included in the conventional clinical treatment repertory[23].Several methods are designed to boost levels of naturally occurring dopamine or improve how the prodrug levodopa works. Others aim to regulate the basal ganglia ircuitry by lowering the over activity of particular brain regions associated with PD, like the subthalamic nucleus. Each is meant to alleviate symptoms[24].

6)Stem cells therapy:-

For a long time, cell replacement therapies have been a promising option for the treatment of Parkinson's disease. However, foetal tissue has limitations as a cell source, pertaining to its availability, the lack of capability for uniformity, and heterogeneity in procedures. As a result, the results of foetal tissue-derived cell transplantation in patients with Parkinson disease have been uneven. Cell-replacement therapies using dopamine neurons created from human pluripotent stem cells have significant benefits over those using foetal cells because to developments in developmental and stem cell biology. In this Review, we examine the prospects and existing constraints of this field of clinical and translational research, as well as the wider range of Parkinson disease symptoms that dopamine cell replacement therapy may be able to treat[25].

It is crucial to understand what factors affect how much symptom relief patients experience following transplantation in order to advance the development of a cell replacement therapy for PD. A list of prerequisites that the grafts most likely need to meet in order to produce a noticeable and clinically significant improvement can be developed based on the findings from clinical trials and studies in animal models: (1) All of the machinery must be expressed by the grafted cells[26].

Because they are undifferentiated, stem cells are unique because they can develop into a wide variety of specialised cells.

Three primary categories of stem cells exist:

• Embryonic stem cells: These cells are pluripotent, which means they can differentiate into any of the several cell types in your body. They are found in embryos, as their name suggests.

• Somatic stem cells, also known as adult stem cells, are used mostly for repair.Though not as many different types of specialised cells as embryonic stem cells, they can nonetheless undergo transformation.

• Induced pluripotent stem cells (iPSCs) are created by genetically altering cells that are already mature. Stem cells are used in stem cell therapy, typically from a donor but occasionally from the patient's own body[27] [28].

Human pluripotent stem cell-derived dopamine neurons, which have a number of benefits over foetal cell-derived dopamine neurons, have been used in cell replacement therapies thanks to developments in developmental and stem cell biology therapies. In this Review, we critically evaluate the potential course of this area of translational and clinical research, discuss its prospects and present constraints, and discuss the wider range of Parkinson disease symptoms that future dopamine cell replacement based on the generation of neurons from human pluripotent stem cells could successfully treat[28] [27].

7)Ayurveda:-

The seeds of Mucuna pruriens L. (DC), which have a long history of safe usage in the disease, are a naturally occurring source of levodopa that is recommended by Ayurveda. Its pharmacokinetic profile is different from synthetic levodopa, according to clinical trials, and thus is anticipated to lessen any unwanted motor problems. Furthermore, its seed extracts have demonstrated neuroprotective advantages unrelated to levodopa[29].

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