A Recent Update on the Dynamics & Challenges in the Treatment of Parkinson's Disease

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Abstract : Parkinson’s disease is a neurodegenerative disorder pathologically characterised by loss of neurons, abnormal α-synuclein deposition in surviving cells, and reactive gliosis in vulnerable areas of the nervous system. This review embodies the systematic overview of the Pathogenesis, Treatment, and future perspectives in treatment and prevention of Parkinson’s Disease and its progression. It also provides an update on the research developments in prediagnostic Parkinson’s disease including how the holistic understanding of the cause and functioning of the disease can help decide strategies for potential neuroprotection & halt the progression in PD. Approaches to successfully modify this diseased condition potentially could modify the natural history of Parkinson’s disease from its very early stages, and might change the way the disease is managed in the future. This review should, accordingly, be of interest to all those working in the field of neurodegenerative disorders.

IndexTerms - Parkinson’s Disease; neurodegenerative disorders; Beta-amyloid plaques, neurofibrillary tangles, degenerative parkinsonism, Lewy bodies.

1. Introduction

Parkinson's disease, one of the most common progressive neurodegenerative disorder, often characterized by a substantial death of dopaminergic neurons in the substantia nigra (pars compacta)5 and is markedly prevailed in senile population of the age of 60 years and above but it can also occur in much younger people. Parkinson’s disease can be characterised by two processes namely cellular degeneration and the biochemical deficiency of dopamine. The resulting dopamine deficiency in the basal ganglia is responsible for a movement disorder, manifested by classical parkinsonian motor symptoms. Though, several agents can be used to treat the motor symptoms associated with dopamine deficiency, there haven’t been proven cases of neuroprotective treatment for Parkinson’s disease lately. Hence, the development of a neuroprotective or disease-modifying therapy that can slow or stop disease progression is the need of the hour in Parkinson’s disease. The compounds that had potential neuroprotective properties in-vitro or in animal models have failed to show any effects on disease progression in clinical trials.

PD is the major cause of degenerative parkinsonism, a clinical motor syndrome characterized by bradykinesia, resting tremor, muscle rigidity, and postural instability. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms and autonomic dysfunction.

The progression of Parkinson's disease is characterized by worsening of motor features; however, as the disease progresses, there is an emergence of complications related to long-term symptomatic treatment. The available therapies for Parkinson's disease only treat the symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the neurodegenerative process. Drugs that enhance the intra-cerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay treatment for motor symptoms.8
2. Pathophysiology of Parkinson’s Disease

The neuropathology of PD is characterized by a specific pattern of dopaminergic neuronal loss in the substantia nigra pars compacta. The substantia nigra is part of the basal ganglia having the principle function of inhibiting unwanted motor activities. When a person wants to make a movement, this inhibition is removed by the action of dopamine. In PD patients, the dopaminergic neurons are lost progressively, hence, voluntary movements become difficult to get initiated due to extremely low levels of dopamine. There is presence of α-synuclein-containing Lewy bodies (LB- which are brain deposits) in the surviving neurons when seen microscopically. Depending on their location, the α-synuclein aggregates are either termed:

(i) Lewy bodies (when in the perikarya) or
(ii) Lewy neurites (when in the neuronal processes).
2.1 Clinical features of PD:

2.1.1 Motor features include:

A disorder of voluntary movement, Parkinson’s disease leads to a gradual slowing up & softening of the voice with a shuffling gait, experiencing difficulty turning over in bed & using an arm particularly for tasks that require rapid alternating movements such as polishing or cleaning and progressively smaller handwriting. Patients with parkinsonism also have a resting tremor which occur when the arms or legs are relaxed, bradykinesia (slowness of movement), limb rigidity, paucity of facial expression, slurred speech and a monotonous soft voice and Lower jaw tremor.10

2.1.2 Non-motor features include:

Primarily, Parkinson’s disease is a motor disorder but it is complicated by cognitive and neuropsychiatric problems with abnormalities in other parts of the nervous system, also involving the visual, olfactory, somatosensory and autonomic systems. These non-motor problems should be taken into consideration & looked upon while examining the patients. It is also found that upto 25 per cent of patients with parkinsonism have the possibility to develop dementia over four years. Dementia, more often occurs in patients with atypical parkinsonian syndromes like progressive supranuclear palsy (PSP) or corticobasal ganglionic degeneration (CBGD).10

2.2. Targeting the prediagnostic phase of the disease:

In Parkinson’s disease, the neurodegeneration starts years before it is clinically diagnosed. There is evidently a great opportunity in the pre-diagnostic phase of the disease wherein disease-modifying therapies could be most beneficial. Pre-diagnostic phase is the one during which the disease process has just started, but hasn’t progressed to manifest the clinical syndrome. Only after the classic motor signs and symptoms have been
emerged (such as bradykinesia, resting tremor, and rigidity), is the diagnosis of Parkinson’s disease made. This is when there is prominent pathology in the CNS with at least 50% of nigral brain cells degenerated.

Since the time the familial forms of PD are identified, with the identification of gene mutations responsible for these familial forms, and the mapping of risk variants for the disease, the understanding of PD has changed. However, all known genes involved in monogenic forms of PD and risk polymorphisms combined explain only part of all PD cases. A portion of “missing heritability” remains hidden that will hopefully become known through the future development of more informative genetic probing techniques. Clinical genetics aims at identifying mutations that cause a specific disorder.

3. The basal ganglia: Its Neuroanatomy and importance in PD

There are two main efferent pathways which lead to the globus pallidus from the striatum, the direct pathway and the indirect pathway. The direct pathway is the monosynaptic pathway which contacts the internal globus pallidus and to the substantia nigra to some extent. The indirect pathway connects indirectly to these regions of the brain through the lateral globus pallidus and the subthalamic nuclei. The modulation of the activity of the circuits is done by the internal globus pallidus and the substantia nigra via the thalamocortical motor pathways which are inhibitory in nature.

Considering the neurotransmitters involved in these circuits, the striatal neurons are mainly GABAergic containing metenkephalin as a co-transmitter forming the part of the indirect pathway along with the presence of D2 receptors.

In the direct pathway, the co-transmitters are dynorphin and substance P in addition to GABA; in the direct pathway, there is presence of D1 receptors here playing an excitatory role. The GABA/enkephalin neurons of the indirect pathway are inhibited on the activation of the D2 receptors.

In normal physiology, dopamine is responsible for inhibiting the indirect pathway to the external globus pallidus further inhibiting the subthalamic nuclei. When there is deficiency of dopamine, which is the case in Parkinson’s disease, there is a decrease in the inhibitory effect of the indirect pathway leading to a greater inhibition of the external globus pallidus resulting in an increase in the activity of the substantia nigra and internal globus pallidus in the subthalamic nuclei to cause an inhibition of the thalamocortical circuit, hence, causing hypokinesia which is characteristic of Parkinson’s disease.

Since dopamine plays a key role in basal ganglia function, proving that its deficiency causes Parkinson’s disease, the symptoms of the disease can be effectively treated by three main approaches:

1. The action of dopamine can be augmented.
2. The action of other transmitters like acetylcholine which counteract dopaminergic function can be modified.
3. Brain grafts, stem cells or neurotrophic factors serving to replace the redundant dopaminergic neurons can be used.

The striatal–substantia nigra network have adenosine as a neurotransmitter. The activation of which, specifically, of the A2 adenosine receptors causes the release of acetylcholine to increase and that of GABA from the striatum to decrease, in vitro; leading to an increased activity of the striatal GABAergic neurons. Dopaminergic function in the striatum is also reduced by activation of the adenosine receptors. Hence, to reduce the motor symptoms, adenosine A2 antagonists are expected to augment the dopaminergic inhibition of the GABA/enkephalin neurons. For the treatment of parkinsonian symptoms, the nonspecific adenosine antagonist, theophylline, has shown clinical evidence to augment the effects of L-dopa.

4. The genetics of PARKINSON’S DISEASE:

According to the research carried out in order to find the genes associated with PD, the following forms of genes were obtained. These are as follows:

4.1 Monogenic forms

1. PARK-SNCA
2. PARK-LRRK2
3. PARK-VPS35
4. PARK-EIF4G1
5. PARK-CHCHD2
6. PARK-parkin
7. PARK-DJ1
8. PARK-PINK1
9. PARK-RAB39B
10. PARK-DNAJC6
4.2 Unconfirmed or unreplicated loci/genes for PD
1. PARK5
2. PARK13
3. PARK11

4.3 Non-PD monogenic disorders that are present with parkinsonism

Many monogenic disorders other than PD form the secondary feature present with parkinsonism. These disorders have great similarities with PD, although being clinically different from it.

Figure 3: Neurobiological diseases showing Parkinsonian symptoms.
5. Treatment or Management of PD:

5.1 Brain transplants: A feasible method to fight PD?

It has been shown that when the foetal mesencephalic tissue is implanted in the striatum of patients with the juvenile form of Parkinson’s disease, there is development of functional axons, thereby, reducing L-dopa dose. Functional dopaminergic neurons are said to develop in the patient brain after tissue transplantation as shown by imaging as well as pharmacological studies. A major ethical objection stands erect here as these transplants require about six to seven foetal brains to reach enough tissue, which can be overcome by the use of brain transplants from domestic animals such as pigs. Even after all this, the chances of neurons surviving the transplantation is only about 20%. The immense use of such transplants can spread viruses and prion infections, even though such xenotransplants have been shown to survive in the human brain.

The need for foetal tissue or xenotransplants can be overcome by techniques viz. the implantation of mesencephalic dopaminergic neurons grown in cell culture or instead of that, the use of human origin stem cells. Trophic factors have been proved to be of importance in the development of neurons and their maintenance in the adult brain. Also, the growth of dopaminergic neurons is stimulated by the glia-derived neurotrophic factor.8
5.2 Deep brain stimulation therapy for PD:

Deep brain stimulation (DBS) is a surgical procedure which implants a device sending electrical signals to the brain with the help of electrodes placed at different locations of the brain, in turn connected to a stimulator device. DBS is used to treat the debilitating motor symptoms of Parkinson’s Disease. Adaptive DBS in Parkinson’s disease uses a fully implanted device and neural sensing, utilizing basal ganglia signals for feedback control.

Deep brain stimulation (DBS) stands to be an effective treatment for Parkinson’s disease (PD) provided the limitations it has that is reduced efficacy for individual patients and preventing application of the technique widely. These limitations can be requirement of a trained clinician for its programming as well as time consuming. Probability of occurrence of dyskinesia as an adverse effect is huge, in response to DBS.
5.3 RESTORATION OF DOPAMINERGIC DEFICITS:

Restoration of striatal dopaminergic tone forms the basis for the treatment of many of the motor symptoms of PD. This is achieved by targeted delivery of dopamine-producing cells, or utilizing the viruses to deliver genes encoding the enzymes required for dopamine biosynthesis into the striatum. Human foetal ventral mesencephalon (VM) tissue grafts in humans have given enough proof-of-concept that cell-based approaches like these can be effective in treating much of the critical features of PD.

5.4 Viral Gene-Delivery Approaches:

Persistent transgene expression has been shown in Adeno-associated virus (AAV) vectors carrying AADC with resultant long-term conversion of levodopa to dopamine in non-human primates. Investigation of the safety of AAV vectors delivering AADC to the putamina of PD patients has been successfully been brought about by Phase I trials.

5.5 Reduction of α-Synuclein Production: 20

The pathological hallmark of PD is manifested by the accumulation and aggregation of α-synuclein. Its role is not understood sufficiently, yet it is of utmost importance in the pathogenesis of PD (and other α-synucleinopathies such as dementia with Lewy bodies and multiple system atrophy). Reducing the synthesis of α-synuclein is one of the mechanisms by which the pathological effect could be prevented. This is attained by RNA interference technologies which involve exogenous introduction of synthetic ribonucleic acid (RNA) molecules to...
trigger selective post-transcriptional silencing of the α-synuclein gene through messenger RNA (mRNA) degradation. This concept can be fairly supported by the silencing of ectopic α-synuclein expression in a rodent model and in SH-SY5Y cells by Lentiviral delivery of a short-hairpin RNA (shRNA) targeting α-synuclein.9

5.6 Increasing α-Synuclein Clearance:

The approach acting as a substitute to targeting α-synuclein, is to enhance its clearance which can be potentially achieved through the following ways:

a. increasing the degradation of α-synuclein intracellularly, through autophagy pathways and for eg. the ubiquitin-proteasome system, or

b. by the use of immune-therapies to clear off the extra-cellular α-synuclein, knowing the hypothesized fact that α-synuclein pathology have the chances to spread between cells in a prion-like fashion.12

5.7 NEUROCHEMICAL BIOMARKERS:

a) Orexin:

A small number of neurons of the dorsolateral hypothalamus express Orexin, is a neuropeptide hormone, also referred to as hypocretin. Orexin, secreted by the lateral and posterior neurons of the hypothalamus, regulates the sleep-wake cycle, cardiovascular responses, heart rate, and hypertension. Because of loss of hypocretin neurons in the hypothalamus, PD patients usually suffer from narcolepsy. Orexin level is associated with the severity of the disease, the concentration of orexin A being lower in PD patients than in healthy individuals. PD patients generally experience Hypophosphorylation and overexpression of glial fibrillary acidic protein (GFAP), hence it is suitable to say that PD is identifiable by elevated GFAP levels as an astroglial marker.5

b) 8-Hydroxy-2-Deoxyguanosine:

Biological molecules are damaged by Reactive oxygen species (ROS) species like O$_2^-$, H$_2$O$_2$, and ·OH, by irreversible reactions which lead to degenerative processes associated with aging. 8-OHdG, is an oxidized form of 8-hydroxyguanine (8-OHG). It is one of the DNA lesions caused by ROS which can possibly be used as a biomarker of DNA damage.11

5.8 New drug:

There are currently only two advanced clinical trials on these disorders which reflect how limited these trials are. Currently, a trial has been investigating the acetylcholinesterase inhibitor Donepezil in patients with PD and mild dementia, after having enough evidence base for Rivastigmine. Cholinesterase inhibitors pose a positive impact on global assessment, cognitive function, behavioural disturbances and daily activities in patients. Atomoxetine, the selective noradrenaline reuptake inhibitor, has manifested improvement in executive function in PD patients without dementia.4
5.9 Transcranial direct current stimulation:

Transcranial direct current stimulation (tDCS), is yet another mode of non-invasive brain stimulation which involves a direct current being applied via surface electrodes on the head for a period of time as opposed to the induction of an electric impulse by the short lasting magnetic field in TMS. The likelihood of modulating cortical excitability and promoting motor learning in healthy adults and motor recovery in chronic stroke has evoked interest in tDCS as an intervention in PD, hence, overcoming the problem associated with deep brain stimulation.3

5.10 Role of LRRK2 kinase in Parkinson’s disease:

Rare genetic Parkinsonism is caused due to mutations in LRRK2 (leucine-rich repeat kinase 2) the cause of which remains unknown. Hyperactivation of the LRRK2 is because of every pathogenic mutation in LRRK2, thus involving treatments to modify the disease. LRRK2 inhibitors have entered phase 1 clinical trials & have shown data emerging on LRRK2 involvement in idiopathic PD which points out that the inhibitors may benefit patients beyond those carrying LRRK2 mutations.1
5.11 NON-DOPAMINERGIC TREATMENTS FOR PD:

Use of Anticholinergics in PD are still the first line therapy for some physicians. Amantadine offers symptomatic control of motor features in patients. The basal ganglia, including the substantia nigra, contain Alpha 2-adrenergic a-2a and 2c receptors distributed within. Drugs like Idazoxan and fipamezole, which are a-2 antagonists act by reducing levodopa induced dyskinesia, thereby extending the duration of action of levodopa in MPTP treated primates. The anti-depressant Mirtazapine, is a-2 receptor antagonist, shows to decrease levodopa induced dyskinesias in PD patients. The basal ganglia receive serotonergic input from the raphe nuclei. Also, levodopa induced dyskinesias in PD patients is supressed by Fluoxetine, a 5HT reuptake inhibitor. Worsening of the motor features of PD is associated with the use of SSRI. A2a receptors, localised on striatal medium spiny neurons, modulate the release of GABA and the adenosine A2a receptor antagonists are potential symptomatic drugs for PD which also affect Ach release from striatal cholinergic interneurons and release dopamine from the nigrostriatal tract. The A2a antagonist, KW 6002, could successfully increase locomotor activity and thereby, potentiate rotational behaviour produced by levodopa or...
dopamine agonist drugs. Even when given after 24–48 hours, the benefits of KW 6002 were additive to levodopa or a dopamine agonist, without resulting in any increase in dyskinesias.13

6. Conclusion
Parkinson’s Disease, till date hasn’t found any solid and ultimate treatment to cure the loss of dopaminergic innervations, and thus, be the saviour of many senile targets of PD. Surely, due to the advent of various new approaches to relieve the patients of PD and the gigantic advancements in science & technology, researchers have come up with novel and innovative solutions enlisted above in this article to address the symptoms occurring due to PD. Parkinson’s Disease is associated with morbidity in the ever-growing senile patients, treatment of which needs to be given utmost care & importance to improve the quality of life of PD patients as it stands to be one of the major neurodegenerative disorders.

References:
15. https://www.meta.org/feed-previews/parkinsons-disease-genetics/aafce3ab-6d9e-42a4-9fdd-01b8c3f82139


17. Hickey, Patrick, Stacy, Mark, The surgical management of Parkinson’s disease, Neurodegenerative Disease Management, 2011/06/01, 10.2217/nmt.11.25

18. Christopher G Goetz, Gian Pal, Initial management of Parkinson’s disease, *BMJ* 2014;349:g6258 doi: 10.1136/bmj.g6258


22. [https://www.healthplexus.net/journal/volume-8-number-1](https://www.healthplexus.net/journal/volume-8-number-1)

