A REVIEW ON PARKINSON'S DISEASE TREATMENT AND ITS MANAGEMENT

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Abstract

Parkinson's disease is the second most common neurodegenerative disorder, and a significant increase in its prevalence in the past three decades has been documented. Environmental and genetic factors contribute to the pathophysiology of this disease, and 5% – 10% of cases have a gentic cause. The diagnosis relies on clinical findings, supported by adequate testing. There is no absolute method to diagnose Parkinson's disease in vivo, except for genetic testing in specific circumstances, whose usefulness is limited to a minority of cases. New diagnostic criteria have been recently proposed with the aim of improving diagnostic accuracy, emphasizing findings that might point to other causes of parkinsonism. The available therapeutic options are clinically useful, as they improve the symptoms as well as the quality of life of patients. After the introduction of levodopa, deep brain stimulation emerged as the second therapy with an important symptomatic impact in the treatment of Parkinson's disease. Non-motor symptoms and motor complications are responsible for a large proportion of disability, so these should be identified and treated. Current scientific research is focused on the identification of disease biomarkers allowing correct and timely diagnosis, and on creating more effective therapies, thus fulfilling current clinical unmet needs. This paper presents an updated review on Parkinson's disease, guiding the readership through current concepts, and allowing their application to daily clinical practice.

Keywords:

Deep Brain Stimulation, Levodopa, Lewy Bodies' Parkinson'Disease/diagnosis, Parkinson disease.

Introduction

Basics of Parkinson's disease

Parkinson's disease (PD), or paralysis agitans, is a common neurodegenerative condition, which typically develops between the ages of 55 and 65 years[1]. This disease was first named and described by James Parkinson in 1817. The progression of this disease is gradual and prolonged. It has a plausible familial incidence, although the estimates of these occurrences are low and usually sporadic[2]. This disease is organized into two classifications: genetic and sporadic. Genetic PD follows Mendelian inheritance. Sporadic PD, which accounts for about 90% of all Parkinson's cases, is a more complex category in which the pathogenic mechanisms that underlie it are not yet fully understood[3]. Nonetheless, it is known that the byzantine interactions of genetic and environmental influences play roles in the determination of sporadic PD[3-5]. Several subtypes of PD exist. Each has its own set of causative factors and susceptibilities, pathology, and treatment courses. General risk factors, symptoms, and pathology will be discussed first, before addressing some of the subtypes.

General risk factors

Research studies have linked theories regarding the outbreak of PD to both environmental and genetic circumstances[6]. These theories propose associations between PD and chemical reactions, neurotoxins, and genetic susceptibility or predisposition[3,7-9]. Environmental determinants positively associated with PD include
factors such as injuries to the head, rural living, pesticides, anxiety and/or depression,and intake of dairy products; whereas physical inactivity, smoking, consumption of
coffee and/or alcohol, and serum uric acid concentration are reported as having an inverse relationship to PD[10]. Though it is undisputed that familial factors play a role in this disease, the extent of heritability is heavily debated. As of yet, 41 different genetic loci have been linked to PD pathogenesis through the completion of 6 large meta-analysis studies[11].
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General symptoms

A precedent for the clinical diagnosis of PD, according to the Movement Disorder Society, is centralized on a motor syndrome, Parkinsonism, and is based on three overriding motor symptoms (MS): bradykinesia, rigidity, and resting tremor[12]. Onset
of motor manifestations usually begins unilaterally with asymmetrical effects enduring on the side of commencement[13].
Symptoms include resting tremor, bradykinesia, gait, speech difficulties, hypophonia, muscle dystrophy, postural deformities and instability[14]. Pain, stiffness or numbness
in limbs, bradykinesia, tremors, a decline in facial expressions, and hypophonia are motor symptoms seen in the early stages of this disease's onset[15]. Late-stage motor features may include motor fluctuations, dyskinesia, gait freezing, and falling. Initial

diagnosis may be made based on evaluation of clinical features of patient history and examination[16]. Positive or negative responses to dopamine agents may also be used in the diagnosis of PD over time[17].
Since motor symptoms are the traditional primary identifiers of PD, common non-motor symptoms have been under-reported, often being overlooked or untreated. While non-motor symptoms are more heavily focused on during advanced stages, they occur during all stages of PD[18,19]. They have the potential to be early biomarkers for PD, with symptoms such as olfactory dysfunction, sleep problems, constipation, and erectile dysfunction often predating the diagnosis of PD by years[20,21]. These symptoms can greatly compromise quality of life (QoL) and daily activities, so typical non-motor treatments are based on improving QoL, with newtreatments being developed, but still needing more research because PD treatments
heavily focus on motor symptoms[22].

General pathology

Biochemical studies show a decrease of dopamine (DA) in the caudate nucleus and putamen; PD is therefore considered to be a disease of the neuronal system, which largely involves the nigrostriatal dopaminergic system[23]. This disease is identified on
the premise of two considerable pathological processes: early selective loss of dopamine neurons, and the buildup of Lewy bodies (LBs) made up of α-synuclein that become misfolded and accumulate in a number of body systems of Parkinson's patients[24].
The central nervous system is composed of groups of various nerve cells which form complex interactions that allow for skillful movement. The substantia nigra located in the midbrain is of essential importance to PD, as nigral neurons give rise to an extensive axonal network which innervates the basal ganglia. Liberation of dopamine, a neurotransmitter, by neurons of the substantia nigra allows for communication with neurons of the basal ganglia. Fine tuning of an organism's movements is possible due to this biochemical interaction. Substantia nigra neurons degenerate progressively, leading to lowered levels of dopamine available for neurotransmission in the corpus striatum. This makes Parkinson's a neurological disorder in which movement is affected[25]. Resting tremor, rigidity, declining balance and motor coordination, and bradykinesia, which is characterized by a creeping slowness of voluntary movement, are all movement-related symptoms of PD[26].
Dopamine has indirect roles in the striatum, which decreases cortical excitation of striatal neurons[27]. Boosts in the physiological state of corticostriatal glutamatergic transmission may possibly be an effect of Parkinsonism impairment of dopaminergic neurotransmission[28]. Furthermore, this may consequently emphasize the imbalance between subsets of striata neuronal systems that regulate the basal ganglia's functional output[29,30].
LBs are fibrillar aggregates composed majorly of α-synuclein. LBs and Lewy neurites are pathologically important to Parkinson's as they serve to be a prominent indicationof the disease, being actively associated with Parkinson's pathogenesis[31]. The
formation of LBs has been considered an explanation to the neuronal degeneration that occurs in PD patients since neuronal loss has been found in predilection sites for

LBs. Of the 70+ molecules that have been identified in LBs, α-synuclein is the most prominent[32]. Immunochemistry of this constituent has uncovered that diffuse cytoplasmic staining cultivates into pale bodies, which are anti-ubiquitin antibodies, by compaction[33]. The peripheral portion of pale bodies give rise to LBs. This abnormality has been identified in 10% of pigmented neurons in the substantia nigra and over 50% in the locus coeruleus in PD[34]. Six genetic PD-associated mutations of
α-synuclein have been discovered[35]. Three mutations related to PD have demonstrated acceleration of α-synuclein aggregation, while an additional three show delay of aggregation kinetics. It is therefore troublesome to provide a unifying mechanism describing how familial PD-associated mutations affect the structure of α-synuclein, and how their accumulation and function link with PD, as there have been several suggestions pointing in this direction. For instance, membrane binding studies propose that a minute number of these PD mutants strongly bind to synthetic membrane vesicles, while others show a weakened ability to bind to the membrane. PD mutations have not been shown to drastically alter the toxicity of α-synuclein oligomers or fibrils, although more recent studies have indicated that the most potent toxic species responsible for PD are oligomers that are formed early on in the disease process. p.A30P is the only mutant that has been found to form faster oligomers and slowed the conversion from oligomers to fibrils. It is plausible that every mutation associated with PD alters α-synuclein biology in various ways, which is possibly responsible for the pathogenesis of this disease.
PD pathology affects more than just the dopaminergic nigrostriatal system. Non-motor symptoms can be better explained when examining the effects of multi-system neurodegeneration. Decades of research point to altered cholinergic neurotransmissions. LBs have been found in the neurons of the nucleus basalis of Meynert, the source of cholinergic innervation of the cerebral cortex. The basal forebrain complex, which provides the principal cholinergic input of the entire cortical mantle, degenerates in PD and can lead to symptoms such as dementia,depression, or apathy. Anosmia and hyposmia are common side effects of PD. While the pathophysiology is not fully understood, it could be related to α-synuclein deposits in the olfactory bulb, medulla oblongata, anterior olfactory nucleus, and limbic rhinencephalon. Progressive, non-linear loss also occurs in serotonergic terminals, although slower than the progressive loss seen in dopaminergic terminals. It can lead to both motor and non-motor symptoms such as depression, tremors, weight loss, and visual hallucinations. Reduced levels of serotonin and its metabolite are found in the caudate nucleus, hippocampus, brainstem, and frontal . Additionally, adrenergic neurons are impacted. One study has shown an increase in α1and β1 receptors, especially in demented PD patients, and a decrease in α2 receptors within the pre-frontal cortex. Disruptions in adrenergic pathways may lead to or worsen dementia .

GBA-associated PD

Common risk factors for PD are mutations in the glucocerebrosidase (GBA) gene, which is a gene that encodes for the lysosomal enzyme. During a clinical study on patients with Gaucher's disease (GD), a rare lysosomal storage disorder, this risk factor was identified. It has been discovered that mutations in the GBA gene are more prominent than in any other implicated genes, including dardarin (LRKK2),

α-synuclein (SNCA), and parkin (PARKIN2), in the majority of the PD population. GD is a recessive disorder in which there is a deficiency in the GBA enzyme. It typically involves the mononuclear phagocyte system in which the lysosomes within macrophage lineage cells become excessively stored with lipids. This disease is induced by bi-allelic variants in the GBA gene, which encodes acid beta-glucosidase (glucocerebrosidase) Manifestations such as hepatosplenomegaly, anemia, thrombocytopenia, and bony involvement are common with this disorder. As of yet, 300 distinct mutations have been pinpointed on this gene. These mutations include point mutations, frameshift mutations, splice-site alterations, and recombinant alleles that embody segments of the pseudogene sequence. Gaucher patients who develop parkinsonian features, dementia, or both, are amid the more atypical and uncommon Gaucher phenotypes. A group of 17 GD and Parkinsonism patients were described in2003. The parkinsonian manifestations were aligned with those of sporadic PD. Many
of these patients were in their 40s when they experienced the disease onset, and most responded positively to levodopa (L-DOPA). The GBA gene in these patients was sequenced and it was discovered that there were 12 different genotypes; the most prominent type being 1 N370S allele, which was found in 14 of the 17 patients, including five N370S homozygotes. Four patients had an autopsy performed on them, which revealed LB inclusions, predominantly in the cerebral cortex and the hippocampus.

Research has shown that the onset of motor impairments among GBA mutation carriers occurs 1.7-6.0 years sooner than in those without mutations. Screening showed that GBA mutations were twice as common in PD patients with an early onset (< 50 years) than those with a late onset. 951 patients were screened for N370S and L444P that had an onset of PD before 51 years of age and it was discovered that 6.7% were carriers for the GBA mutation, which is equivalent to the prevalence of patients with homozygous or heterozygous PARK2 mutations. It was also found that GBA mutation carriers developed clinical symptoms earlier than non-mutation carriers when comparing with patients who developed PD before 50 years of age.

Analyses from a study screening for GBA mutations found that GBA carriers were primarily male, had greater occurrences of cognitive dysfunction or dementia, and experienced hallucinations more frequently (not associated with drug treatment) when compared to patients without GBA mutations. A second study recorded that GBA mutation carriers with PD more frequently suffer dementia than non-carriers. The UPDRS, mini-metal state examination, and Hoehn and Yahr staging scales did not detect any noteworthy differences in the magnitude of PD manifestations or the rate of disease progression between GBA carriers and non-carriers. However, several other studies have documented greater rates of cognitive decline, bradykinesia, olfactory dysfunction, and less rigidity correlated with GBA mutations. A German PD study found that GBA mutation carriers have higher frequencies of dementia, neuropsychological disturbances, and autonomic dysfunction, when they compared 20 GBA mutation patients with 20 patients without the mutation.

Early-onset

The incidence of PD increases with age, with an incidence of 0.5 per 100,000 for people below 40 years old compared to the overall incidence of 13.4 per 100,000 for all ages. Early-onset PD is the development of symptoms in those below 60 years old.

It can be divided further into juvenile PD in those younger than 21, and young-onset PD if between the ages of 21-40. Early-onset PD is attributed to genetic factors, rather than environmental. Juvenile PD is rare, but worth mentioning. Its genetic mutations can cause further distinct types of PD. For example, the mutation of ATP13A2 causes Kufor-Rekab syndrome, which is a specific juvenile PD that has less than 50 cases reported to date. Early-onset PD differs in presentation of symptoms and responsiveness to treatment than late-onset PD. With early-onset PD, bradykinesia and rigidity are more likely to be the presenting symptoms, rather than gait disturbance, when initially treated. Early-onset has a slower disease progression and is more likely to develop L-DOPA-related dyskinesia, so dopamine agonists are frequently chosen as the initial treatment options over L-DOPA. However, new evidence suggests that L-DOPA does not necessarily need to be avoided in treatment of early-onset PD. This will be discussed in the dopaminergic medications section below.

Parkinson's DiseaseTreatment

The development of neuroprotective drugs for PD is an important unmet medical need, since this disease progressively impair the patients' quality of life and functionality in activities of daily living. The identification of new therapeutic targets is therefore of great importance. Although different medications and therapies for controlling PD symptoms are currently available, no cure for PD exists. The development of treatments for PD, based on patients' symptoms and needs, vary from different medications to rehabilitation or even surgery. PD includes different clinical entities observed in several studies investigating the existence of PD subtypes. A cluster analysis permits to identify distinct PD subtypes according to the relevance of both motor and non-motor symptoms and select therapeutic approach according to cluster .

pharmacology

The most common therapy for PD includes different commercially available medications that treat the lack of dopamine in the SN. These medications cantemporarily alleviate PD symptoms in different ways by enhancing dopamine level, mimicking the role of dopamine or inhibiting dopamine oxidative metabolism, which leads to the generation of reactive oxygen species . Formation of protein aggregates that lead to neuronal cell death is another important target for PD treatment. Among different PD medications, levodopa (L-dopa, L-3,4-dihydroxyphenylalanine) is an effective drug. Levodopa is the immediate metabolic precursor of dopamine which is produced by TH from L-tyrosine. In the dopaminergic neurons, dopa-decarboxylase converts levodopa into dopamine. The orally taken levodopa can be decarboxylated in peripheral sites before reaching the CNS. Therefore, levodopa is available in combination with carbidopa or benserazide that are peripheral inhibitors of Dopa decarboxylase, but do not pass through the BBB. Unchanged levodopa in the presence of decarboxylase peripheral inhibitors can penetrate into the CNS and is used as a precursor of dopamine .

Levodopa, is more efficiently transformed into DA after vesicle storage by the serotonergic neurons, rather than the dopaminergic ones of the nigrostriatal system. Since the serotonergic distribution throughout the brain is very different than the

dopaminergic one, this causes the well-known side effects of L-DOPA therapy and reduces its efficiency as a drug .
Sinemet was the first brand of carbidopa/levodopa combination in the pharmaceutical market . Rytary and duopa are two newly approved medications for PD by the Food and Drug Administration (FDA). Xadago (safinamide) is recently approved medication for PD patients who do not benefit from levodopa/carbidopa. Rytary is manufactured by Impax Laboratories as an oral capsule containing carbidopa-levodopa together with entacapone to prolong its effects. Doupa produced by AbbVie Company is used for the treatment of motor fluctuations in advanced PD. Dopa is an enteral gel made of levodopa-carbidopa that is pumped to intestines .
A group of dopamine agonists are agents that bind to the dopaminergic post-synaptic receptors and trigger the same signal as dopamine itself. This group include pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, rotigotine, and apomorphine hydrochloride .
Inhibitors of MAOB – selegiline and rasagiline are also available as PD medications. Monoamine oxidase isoforms, including MAOA and MAOB, located on the outer membrane of mitochondria are involved in the oxidative deamination of biogenic amines, such as neurotransmitters and xenobiotic amines, e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The MAOs have a significant effect on the course of PD, because they are involved in the metabolism of dopamine. Oxidative metabolism of dopamine in the dopaminergic cells of SN by MAOs leads to ROS generation, oxidative damage and cell death . Moreover, MAOB catalyzes the conversion of MPTP into 1-methyl-4-phenylpyridine (MPP+) which is responsible forparkinsonism in intravenous drug . Selegiline and rasagiline can protect neurons against oxidative damage induced by dopamine metabolites diminishing MAOB activity. Moreover, several substances, such as entacapone and tolcapone that inhibit catechol-*o*-methyl transferase (COMT) are available as alternative PD medications. These two medications block the conversion of levodopa into methylated levodopa. Therefore, inhibition of COMT activity by these medications can extend the existence of functional levodopa preventing its degradation .
Additionally, some other chemicals can be considered as potential PD medicines. Rapamycin can be a useful treatment for PD as an up-regulator of autophagy. Rapamycin induces autophagy in cells by inhibition of a specific kinase activity called mTOR. Autophagy is a potential target for PD treatment, since it initiates the clearance of protein aggregates and inhibits apoptosis . Adenosine A2A receptor antagonists, such as caffeine also reduces the risk of PD. Transgenic mice with mutant α-syn and deleted adenosine A2A receptor genes are protected against PD. Thus, A2A receptor antagonists are potential candidates for prevention and treatment of PD .
Formation of protein aggregates that leads to neuronal cell death is a promising target for PD treatment. In January 2015, Neuropore Therapies has announced phase I clinical trial of a new drug, NPT200-11 (UCB-1332) that inhibits oligomerization of α-syn . Another potential drug modulating the aggregation of α-syn blocking or reducing the conversion of monomers to oligomers or later on to fibrils is ANLE138b .
Several promising compounds are under development and/or in preclinical testing that may enhance autophagy of α-syn. Recent screening of compounds protecting cells from α-syn induced neurodegeneration identified a non-selective phosphodiesterase (PDE) inhibitor dipyridamole. Importantly, PDE1 inhibition also protects dopaminergic neurons from α-syn induced degeneration in mouse SN. PDE inhibitors are currently at preclinical . Another antiaggregation compound – a natural product squalamine displaces α-syn from the surfaces of lipid vesicles, thereby blocking the

first steps in its aggregation process. Furthermore, squalamine suppresses the toxicity of α-syn oligomers by inhibiting their interactions with lipid membranes .

Surgery

Deep brain stimulation therapy is rarely used for certain types of brain-related disorders including PD, dystonia, obsessive-compulsive disorder and treatment resistant depression . When PD symptoms are very severe and medications cannot moderate them, surgery and DBS can be considered as the final options for the treatment. It involves sending electrical impulses to certain parts of the brain (usually SN or globus pallidus, which communicate with the SN) by a neurostimulator devicethat is a brain implant known as a 'brain pacemaker.' The target area of DBS is usually the subthalamic nucleus (STN). The stimulation of the dorsolateral STN border alongside the surgery can improve its efficiency . Later it was found that stimulation of caudal zona incerta (cZI) can be more effective with fewer complications after the surgery . Stimulation of neurons may also lead to neurogenesis and neuroplasticity and thus can improve for a long time motor problems, such as dyskinesia and tremor, and all other levodopa-responsive symptoms, for a long time. However, there are two problems with DBS, namely a 3- to 6-month waiting period required for optimal results and the possibility of brain infection .

GeneTherapy

The development of gene therapy of PD has made a major progress in a recent decade. Advanced PD does not give a good response to levodopa therapy. Broaden loss of dopaminergic neurons is accompanied by reduction in aromatic amino acid decarboxylase (AADC) levels that converts L-DOPA to dopamine. After successful preclinical studies, adeno-associated viral vectors carrying human AADC gene are recently delivered into putaminal neurons and subthalamic nucleus of PD patients. In this method, sufficient amount of dopamine production can be controlled by taking adequate levodopa dose. Orally taken levodopa can be converted into dopamine by AADC and sooth PD symptoms . Safety and efficiency of the method have been proven over 4 years by annually PET imaging from patients who received specific dosages of AAV2-. Another target for gene therapy in PD is glutamic acid decarboxylase (GAD) that facilitate production of GABA in GABA-ergic neurons in the subthalamic nucleus. GABA as an inhibitory neurotransmitter regulates muscle tone and improve motor functions . Lack of dopamine in PD causes activation of the subthalamic nucleus and unnecessary muscular responses that GABA by its inhibitory effect can significantly improve. This method can be compared with DBS that by sending electric shocks to subthalamic nucleus reduces its hyperactivity and improve motor impairment . The human trial of this method was performed by bilateral injection of AAV2-GAD in the subthalamic nucleus of patients with advanced PD. This approach has shown safety and efficiency, although it needs more investigation to be considered as a treatment .

Therapeutic effect of glial cell line-derived neurotrophic factor (GDNF) on neuronal function in non-human models of PD encouraged scientists to inject it directly into putamen of PD patients. This surgery helped patients with improved movement, reduced dyskinesia and increased dopamine storage in the putamen . Therefore, GDNF is a possible option for gene therapy. Neurturin gene is another candidate for

PD gene therapy. Neurturin is a neurotrophic factor important for survival anddifferentiation of dopaminergic . The human trial of this factor was conducted by bilateral injection of vector AAV2-neurturin (CERE-120) into the putamen biomarkers patients with advanced PD . Injected neurturin cannot spread into SN and play its therapeutic role because of vast axonal transport defects in PD patients. Another consequence of this method may be the accumulation of α-syn that leads to downregulation of neurturin expression .

Summary

PD is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. Striatal dopamine depletion has been identified as the major cause of the disorder's motor symptoms, which include resting tremor, "cogwheel" rigidity, and bradykinesia. Nonmotor symptoms include sleep disorders, depression, and cognitive changes.
The differential diagnosis of PD should include a comprehensive history and physical examination.Identifying diseases that have presentations similar to that of PD is an important component of the diagnostic process. There are no definitive tests to confirm a diagnosis of PD.The UPDRS is the most commonly used scale for assessing the clinical status of PD patients.
The primary goal in the management of PD is to treat the symptomatic motor and nonmotor features of the disorder, with the objective of improving the patient's overall quality of life. Therapies that slow the progression of the disease or provide a neuroprotective effect have not been identified.
In the next issue of P&T, part 2 of this five-part article will discuss the pharmacological management of PD, with a focus on the use of dopaminergic agents.

Conclusion

Parkinson's disease is one of the most common neurodegenerative diseases affecting the aging population and is associated with an increased morbidity and mortality. Awareness of the disease manifestations, the treatments, and the progressive long-term course of the disease is necessary for the optimal management of the cases. Tremendous progress has been made in understanding the neuropathology of PD and its progression throughout the nervous system. However, none of these treatments is curative. PD remains a progressive disorder that eventually causes severe disability due to the increasing severity of treatment-resistant motor problems and non-motor symptoms. Modifying factors that lead to the disease progression and in furtherdelaying its disability are the key unmet needs to be addressed by the current and future research efforts.

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