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Parkinson's Disease (Pathogenesis and Its Management): An Overview

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Abstract

Parkinson's disease (PD) is an idiopathic neurodegenerative disorder which has its incidence mainly in elderly aged humans. Loss of dopaminergic neurons especially in the substantia nigra, presence of α-synuclein Lewy bodies, mitochondrial dysfunction are the main pathological implications that plays pivotal role in both sporadic and familial forms of the disease. As PD affects older adults mostly in economically developed countries and worldwide aging populations there is an urgent need to develop strategies for the health care of individuals with PD. Epidemiological studies help in better understanding of the risk factors for PD and also helps in management of the disease and effective planning of medical services. In this present review article current understanding of Pathophysiology, Risk factors of PD were presented and the latest therapeutic approaches were discussed.

Keywords: Parkinson's disease; Neurodegenerative disease; Mitochondria

Introduction

According to World Health Organization Neurodegenerative diseases are the leading cause for death in the elderly, and it predicted that by 2040, neurodegenerative diseases will go to second place in overall cause for death after cardiovascular diseases [1]. Parkinson's disease (PD) sometimes called "paralysis agitans," was first recognised in early 1800's by the physician after whom the disease is named. Parkinson's disease which is an idiopathic degenerative disease of nervous system affects both non-motor and motor system. PD is a progressive chronic neurodegenerative disorder mostly affecting older persons but it can also occur in younger people. But, PD is highly uncommon in young people and its incidence is very less in people under 40 years of age. Men are at more risk than women, men are 1.5 times more likely to develop PD than women. This difference is slightly varied from based on their geographical location for example PD is seen more in people with an older age in Western populations than Eastern countries. However, further studies are required confirm the ethnic differences in PD risk.

Estimates suggest that PD is expected to rise at an accelerated rate over the next 20 years in the aged individuals and continues as an important health issue with significant economic drain due to its direct and indirect healthcare costs. The economic and psychological burden is proved to be highly significant in developed nations where the average lifespans of the people are continuously increasing due to medical advancements.

Therefore, there is an urgent need in developing effective treatments for PD through research in medical and pharmaceutical fields.

Pathophysiology

Aggregation of alpha synuclein (α-syn)

Investigating the role of the protein alpha synuclein (α-syn) in the pathophysiology of Parkinson's disease (PD) has begun in 1997. For the first time scientists found that a missense mutation in α-syn gene causes familial PD [2]. In the same year other studies proved that α-syn as one of the main components of Lewy bodies [3], which is the important neuropathological feature of PD [4]. The aggregation of α-syn causes a spectrum of disorders termed as synucleinopathies and a hypothesis has been put forward that α-syn aggregation results in toxicity through a gain-of-function mechanism. But, some studies proved that the α-syn plays an import role in a diverse range of essential cellular processes such as response to cellular stress and the regulation of neurotransmission.

α-synuclein immunoreactive protein aggregation in some selectively vulnerable neuronal types is crucial for the onset of sporadic Parkinson's disease. The initial misfolding and subsequent aggregation of α-syn occurs in the enteric nervous system and/or the olfactory bulb which are exposed to potentially hostile environment. Generally these inclusions occur in cell somata in the form of spherical Lewy bodies [5-8], as thread-like Lewy neurites or elongated spindle-shaped. Whereas in axons and dendrites [9-12], these develop as pale bodies [13], which are granular or dot-like or sometimes in punctate shape aggregates [14,15].

Distribution pattern of α-syn aggregates in the nervous system of PD patients

Development of α-syn aggregates generally progresses caudo-rostrally through lower brainstem regions such as lower raphe nuclei, dorsal motor nucleus of the vagal nerve, magnocellular nuclei, locus coeruleus then into midbrain tegmental nuclei mainly in the region of dopaminergic neurons of the substantia nigra and noncortical centres of the forebrain such as amygdala, magnocellular nuclei of the hypothalamic tuberomammillary nucleus, basal forebrain, midline and intralaminar nuclei of the thalamus. Finally, it reaches to the cerebral cortex. [16-22].

Spreading of α-syn along axonal connectivity

Recent studies had proved that the brain regions and nerve cells that

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become sequentially involved in PD are anatomically interconnected, even over long distances, and the physical contacts between nerve cells and axonal transport are involved in PD pathogenesis [23-25]. Many studies have proved the retrograde axonal transport of α-syn from peripheral nervous system to the central nervous system (CNS) [26], However the connections between the enteric nervous systems (ENS) and CNS by the vagus nerve play major role in the progression of PD [27,28]. Recent large-scale epidemiologic analysis of vagotomies that were performed to treat peptic ulcers have showed the involvement of ENS in the PD [29].

Finally, we can conclude that the misfolded and aggregated α-synuclein seeds can spread trans-synaptically through multisynaptic pathways and can function in a strain-dependent manner as self-propagating pathogens in disease progression [30-54]. The PD related damage occurs mainly in the superordinate centres of the limbic, somatomotor and visceromotor systems.

Cortical atrophy

Cortical atrophy is also one of the primary clinical manifestations in patient with PD. Till now three subtypes of cortical atrophies were identified in non-demented Parkinson's disease patients. They are frontal and occipital cortical atrophy especially in younger disease onset, parieto-temporal atrophy in worse cognitive performance and finally in patients without detectable cortical atrophy. These atrophy patterns help in identifying the prognosis of the disease.

Mitochondria Dysfuntion

Mitochondrial dysfunction is associated with PD. Dysfunction of mitochondria may be due to mutations in genomic DNA effecting Mitochondria or bioenergetic defects or Mitochondrial DNA mutations or Morphological and physiological changes affecting the dynamics of the mitochondria such as changes in fusion or fission, size and morphology, trafficking or transport, movement of mitochondria, transcription, and the presence of altered or misfolded proteins.

Mitochondrial respiration in PD

Mitochondrial respiration alterations are involved in PD. Some compounds like Rotenone, trichloroethylene etc., inhibit complex I of mitochondria reduces movement of mitochondria, increases generation of reactive oxygen species (ROS), resulting in dopaminergic neurodegeneration suggesting that mitochondrial dysfunction plays an important role in PD [55,56]. In the substantia nigra, in the skeletal muscles and platelets the activity of complex I is impaired in PD patients [55,57,58]. Recent studies have shown that post translationally modified α-synuclein with high affinity binds to translocase of outer membrane (TOM20) of mitochondria and inhibits the transport of proteins into the mitochondria. This abnormal α-synuclein-TOM20 interaction was observed in nigrostriatal dopaminergic neurons in the post-mortem of brains from PD patients [59].

Genetic mutations affecting mitochondria

Generally Parkinson's disease is well-thought-out as a non-genetic disorder where about 15% of entities with PD have a first-degree relative having the disease and for remaining 5% of individuals it's because of mutations in some specific genes. Mutations in certain genes affecting mitochondrial structure and function are known to play a key role in familial PD. DJ-1, α-synuclein, Parkin, LRRK2, NURR1, PTEN-induced kinase1 (PINK1), vacuolar protein sorting 35 (VPS35), UCHL-1 and HtrA2 have pathogenic mutations which directly or indirectly affect mitochondrial normal functions has been observed in familial PD [55,60,61]. Juvenile Parkinsonism is mainly caused by Parkin which is an autosomal recessive disorder. Parkin gene encodes an enzyme E3 which is called as ubiquitin protease ligase. By these it can be concluded that mutations in PINK1 and Parkin causes defects in the functioning of mitochondria and also mitophagy [62]. Transcriptional up-regulation of PARK2 gene in response to damage of mitochondria leads to the loss of vacuolar protein sorting 13C (VPS13C) function this leads to the early onset of autosomal-recessive Parkinsonism [63].

Recent studies have shown that heterozygous mutations in glucocerebrocidase (GCase) gene is also frequently found in patients with PD [64,65]. Mutations in Leucine-rich repeat kinase 2 gene has a major role in monogenic PD in several populations [66,67].

Lysosomal dysfunction

A number of different types of mutations in PARK-genes are associated with the mitophagy or autophagy–lysosome pathway [68,69]. Lysosomal p-type ATPase13A2/PARK13 [70], alpha-synuclein (PARK1, PARK4) are fully or partly degraded by lysosomes [71,72], the leucine-rich repeat kinase LRRK2/PARK8 are crucial for the maintenance of autophagy–lysosome pathway function [73] and lysosomal glucocerebrosidase [74,75].

DNA Methylation in PD

Many researchers opined that PD is a consequence of various genetic variants along with complex environment–gene interactions and age-related changes and presdisposing factors [76]. Recently few hypotheses were proposed that the altered DNA methylation also play a key role in the pathogenesis of PD.

Jowaed et al. [77] reported DNA methylation in the transcriptionally active intron1 of SNCA in PD patients' brains. Whereas Cai et al. and De Mena et al. [78,79] reported that there is no alteration in the methylation levels of SNCA gene promoter and Tan et al. [80] found that the methylation levels of the leucine-rich repeat kinase 2 was not altered.

Dysregulation of iron metabolism

Recently Brain iron homeostasis recognized as one of the potential target in the development of drug therapies for neurodegenerative disorders. Actually Iron plays a major role in maintaining normal physiological functions in the brain through its participation in key cellular functions such as myelin synthesis, mitochondrial respiration and neurotransmitter synthesis. But, excess iron causes oxidative damage by free radical formation.

In recent studies a correlation between the accumulation of iron in glial cells and neurons of the Substantia Nigra with the severity of PD disease is identified [81]. Moreover, iron induces the conversion of α-synuclein to the β-sheet from the α-helix conformation which is a characteristic of the Lewy bodies present in SN of PD patients [82].

Iron chelation efficacy that reduces iron levels in PD has been investigated and this prevented toxicity in mouse model of PD [83]. But the main difficulty in using iron chelation is caused by the inability of large iron chelating molecules such as desferrioxamine in penetrating the Blood brain barrier. However relatively low molecular weight compounds such as clioquinol has been effective in treating dementia and Parkinsonism phenotypes in mouse [84,85].

A Risk Associated with Living in Rural Areas

Recent studies have considered the exposure to pesticides,

well water use, especially in rural living scenarios as risk factor for developing Parkinson's disease. People having Farming as an occupation were significantly associated with PD, but many studies have shown that there is no increased risk of PD with rural or farm residence or well water use. These observations conclude that Parkinson's disease is linked with occupational exposure to herbicides and insecticides and also farming; however the risk of farming cannot be presented by pesticide exposure alone.

Symptoms

Motor symptoms

PD is associated with bradykinesia (slow movements), resting tremor (initially unilateral), rigidity, postural instability and shuffling gait. PD symptoms are progressive and the progressions are highly variable. Other symptoms include blurred vision, decreased eye blink rate, dystonia, impaired upward gaze, kyphosis, masked facial expression (hypomimia), speech impairment, stooped posture, palilalia (repetition of word or phrase) or hypophonia (increasingly soft voice), etc. Around 25-60% of PD patients experience freezing of movements after several years from PD onset [86].

Non-motor symptoms

Non-motor symptoms of PD pose greatest challenges to quality of PD patient's life. These include autonomic nervous system failure, cognitive changes, neuropsychiatric changes, sensory and sleep disturbances. Recent studies have shown that around 90% of PD patients have non-motor symptoms during the course of PD. Problems with decision-making, memory retrieval, multi-tasking and visuospatial perception can also be seen in patient suffering with PD.

Probability of occurrence of hallucinations and Psychosis in PD patients is high. The most common psychotic symptom is visual hallucinations. Almost forty percent of drug-treated PD patients undergo some form of psychosis. All the anti-parkinsonian medications are shown to induce some form of psychosis.

Dementia of PD occurs in the later stages but early onset of dementia is seen in patients with a family background of PD. Mood disorders such as anxiety, depression and apathy also occur in PD patients. Mood disorders are the most troublesome non-motor symptoms in both the early and late PD patients and anxiety is the most frequent psychiatric mood disorder. Abulia (loss of ability to think or act) and apathy (loss of motivation) can also occur. Sleep disturbance, frequent waking during the night, early morning awakening, Rest tremors and sleep attacks. All these symptoms seriously erode quality of life of the PD patients. Autonomic disturbances such as constipation, dysphagia, fecal incontinence, orthostasis, urinary difficulties, sexual dysfunction, nocturia and urge incontinence sialorrhea (excessive salivation) are not uncommon in PD patients. PD also alters skin health by affecting micro RNAs that regulate protein-coding genes that are involved in wound healing and angiogenesis. Olfactory dysfunction and sensory symptoms of pain are also found in PD patients.

Diagnosis

Currently structural and functional neuroimaging studies such as 18F-fluorodeoxyglucose-positron emission tomography 18 (FDG-PET), single-photon emission computed tomography, PET-computed tomography and magnetic resonance imaging are being employed in clinical diagnosis of neurodegenerative diseases [87].

Phosphorylated α-synuclein is associated with abnormal EEG wave spectra of brains in PD patients. Hence, *in vivo* EEG quantitative measures can be used as a valid biomarker of cognitive abnormalities in PD [88]. Cerebrospinal biomarkers are not yet identified for PD. However, in recent studies it was found that there is an increase in α-synuclein levels in L1CAM-positive vesicles in plasma of PD patients when compared with healthy individuals. Therefore, CNS-derived extracellular vesicles have the potential to be developed as PD biomarkers [89]. Generally α-Synuclein is biochemically measured using ELISA or by immunoblots [90].

Treatment

Nuclear receptor Nurr1 plays an important role in the development of dopamine (DA) in midbrain neurons making the Nurr1 as a target for PD. *In vitro* and *in vivo* studies shown that Nurr1 gene therapy and Nurr1 activating compounds improves DA neurotransmission and protects DA neurons from toxic effects of neuroinflammation mediated by microglia or environmental toxins [91]. The retromer pathway has been emerged as one of the most efficient pathway implicated in PD. Deficiency of or mutation of VPS35 leads to the aggregation and accumulation of α-synuclein with degeneration of dopaminergic neurons and also causes mitochondrial dysfunction. Hence retromer pathway is a promising target for PD [92,93].

Dimethylfumarate (DMF) and monomethyl fumarate (MMF) offers neuroprotection through Nrf2-mediated antioxidant pathway and anti-inflammatory [94]. MMF's neuroprotective effects will not involve the inhibition of mitochondrial functions, so oxidative damage due to mitochondrial dysfunction which is one of the main causes for the pathogenesis of PD can be averted by using MMF hence MMF can be used in developing a new therapy for PD.

Targeting synucleinopathies

Targeting of α-syn accumulation, such as its aggregation, synthesis, and clearance, can help in disease modification and lowering the symptoms and recent approaches focused on α-syn such as active and passive immunotherapy [95], degrading enzymes [96], anti-aggregation compounds [97], α-syn siRNA delivery [98], autophagy enhancers [99] and molecular chaperones [100]. Stimulating neurogenesis [101] and Regenerative therapy using stem cells [102] has gained much attention.

Oral L-dopa therapy

In all the stages of PD and with almost all types of complications treatment with L-Dopa is recommended. Uptake of L-Dopa into blood from the duodenum and to the brain competes with the uptake of neutral amino acids hence L-Dopa preparation should be 1 h before or after a meal.

Dopamine agonists

Dopamine agonists are used mainly in the early stages of PD as mono therapy or adjunct therapy (2a) along with L-Dopa therapy in the intermediate state of PD and along with L-Dopa (2b) in the advanced state PD. Five ergot and five non-ergot-derivates totally ten dopamine agonists are available for the treatment of PD. Ergot dopamine agonists include α-dihydroergocriptine, bromocriptine, cabergoline, pergolide and lisuride and piribedil, pramipexole, ropinirole and rotigotine are the non-ergot derivates. The main disadvantage of dopamine agonists especially will in the advanced stages of PD which results in the accelation of cognitive impairment or dementia, hallucinations.

Deep brain stimulation

Deep brain stimulation (DBS) especially in the subthalamic nucleus

(STN), ventral intermediate nucleus (VIM), and globus pallidus pars internus (GPi) has been developed especially for the treatment of the motor symptoms of PD mainly for tremors at rest which is resistant to pharmacotherapy.

Other compounds

Caffeine: Many studies have shown that Drinking coffee reduces the risk of developing PD [103]. Caffeine intake has shown symptomatic benefits in PD patients [104].

Inosine: Inosine is a precursor molecule of urate and its administration leads to increase in serum urate levels. Elevated Urate levels increases the antioxidant activity in substantia nigra pars compacta dopaminergic neurons and protects against 6-OHDA toxicity [105]. Some studies proved that Inosine is safe and triggers urate levels in cerebro spinal fluid and serum which decelerates PD progression [106].

Nicotine: Epidemiological Studies during the last few decades have shown an inverse relation between PD susceptibility and tobacco consumption. PD is found to be less prevalent among smokers than non-smokers [107]. Nicotine up-regulates anti-apoptotic proteins which prevents or slows down the neurodegeneration [108]. Nicotine activates the enzymes of the cytochrome P450 family which detoxifys neurotoxins [109]. Studies on non-human primates have shown that Nicotine protects from toxin-induced nigrostriatal degeneration [110].

Herbs: Many herbs have shown potential in the treatment of PD symptoms or to reduce the PD progression. Herbs such as Acanthopanax (*Eleutherococcus maxim*), Alpinia (*A. galanga*), Astragalus, Camellia (*C. sinensis*), Cassia (*Cinnamomum fragrans*), Chrysanthemum (*Chrysanthemum morifolium*), Cistanche, Cuscuta (*Cuscuta L.*), Fraxinus (*Fraxinus excelsior*), Gastrodia (*G. elata*), Ginkgo (*Ginkgo biloba*), Gynostemma (*Gynostemma pentaphyllum*), Polygonum (*Polygonum multiflorum*), Pueraria (*Pueraria mirifica*), Rhodiola (*Rhodiola rosea*), Scutellaria, Tripterygium (*Tripterygium wilfordii*), etc. have potential neuro protective properties.

Currently there is no treatment that could completely cure Parkinson's disease, but very few treatments are available that help in relieving the symptoms and maintaining the quality of life. The conclusions published in the journal *Nature Communications*, present a better understanding and provide scope for further research towards a possible cure or treatment of Parkinson's disease. Despite of the advances in understanding the causes of familial forms of this disease, the idiopathic form of Parkinson's disease which is the most prevalent still remains a mystery.

Conclusion

PD is one of the most common neurodegenerative diseases mostly seen in later ages of life. A combination of environmental and genetic factors is responsible for the abnormal protein aggregation in some specific group of neurons, leading to their dysfunction and eventually death. Genetic factors involving the methylation of DNA affecting genes in the function of mitochondria are found to be one of the most important causes for the pathogenesis of PD. Identifying biomarkers for early detection of PD in humans will undoubtedly improve the early stage therapeutics like immunotherapy. However, efforts in the development of effective alternative treatments for PD and related neurodisorders have increased recently. Logical combination of therapies can be a potent approach for treating synucleinopathies. In the next decade we can see a rise of personalized medicine for the treatment of PD, including familial and sporadic with disease-modifying approaches.

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