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RECENT ADVANCES IN THE MANAGEMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder more commonly found in elderly between the ages of 60-65. Rigidity, bradykinesia, tremors and postural instabilities are the characteristics of PD. The symptoms of PD can be classified into; motor symptoms (speech difficulties, dysphagia, dystonia, tremors etc.) and non-motor symptoms (cognitive impairment, anxiety, sleep disorders etc.).The etiology of PD is still unknown, however it is considered to be caused by a blend of various genetic and environmental factors. The hallmark of PD is the presence of alphasynuclein containing lewy bodies in the substantia nigra region of the brain. The main cause of PD is due to degeneration of dopaminergic neurons in the brain which can be due to various reasons like toxicity caused by specific proteins, mutations, exposure to toxins etc. The drug treatments only focus on symptomatic relief and temporal improvement is limited. Hence in order to achieve significant results on both motor and non-motor symptoms multiple new approaches like ablative surgeries, gene editing, identification of therapeutic targets are being considered to enhance the management of PD.

KEYWORDS: Parkinsonism, lewy bodies, α-syn toxicity, familial PD, CRISPR, therapeutic targets.

INTRODUCTION

Parkinson's disease is described as a progressive neurodegenerative disorder characterized by bradykinesia, tremors, rigidity, and gait dysfunction. It is more commonly found in elderly patients between the ages of 60-65. PD was first described by James Parkinson in his "Essay on the shaking palsy" in 1817.[1] Dementia, hyposmia, gastrointestinal alterations are a few of many impairments caused by PD. The pathogenesis of PD includes the existence of α-synuclein-containing Lewy bodies in the substantia nigra region of the brain in the form of

filamentous cytoplasmic inclusions. Lewy bodies are formed due to the phosphorylation and fibrilization of α-synuclein and induce neuron death.[2-4] The reduction in the facilitation of voluntary movements in the body is mainly due to the depletion of DAnergic neurons in the pars compacta of the substantia nigra. During the progression of PD α-synuclein buildup becomes more extensive in the brain.[5] Lewy bodies are observed in definite parts of the CNS (basal ganglia, the olfactory bulb, the locus coeruleus, the dorsal motor nucleus of the vagus, the intermediolateral nucleus in the spinal cord) and PNS (celiac ganglia and enteric nervous system) in patients suffering from PD.[6-8] Sleeping disorders, meek tremors, soft speech, postural strain, decreased limb motion, loss of focus, depression (with no obvious reason) may mark the onset of PD.[9]

CLINICAL SYMPTOMS OF PD

Motor symptoms

Prime motor function impairments include bradykinesia, resting tremors, rigidity, and postural difficulties. In addition to these, secondary motor symptoms such as gait impairments, micrographia, speech difficulties, dysphagia, dystonia, and precision grip impairments deteriorate the quality of life of patients.

Non-motor symptoms

The non-motor symptoms (NMS) consist of, autonomic symptoms (orthostatic hypotension, bladder disorders, erectile impotence) sleep disorders (rapid eye movement disorders, insomnia, vivid dreaming), and neuropsychiatric symptoms (cognitive dysfunctions, depression and dementia).[10-11]

A majority of NMS of PD can occur for years, if not decades, remarkably before the occurrence of motor symptoms. But even so the occurrence of NMS during the disease progression is reported in almost 90% of patients.[12] Since NMS do not react to dopamine treatment and also motor symptoms, it can pose many difficult problems to standard of living and ongoing treatment in PD.[13] In addition to this PD therapy can also aggravate or trigger NMS.

Etiology

The etiology of PD is not known however it is supposed to be caused due to a blend of various factors like genes or surrounding environment.[14-15] In comparison to subjects in control or regular populace, the ‘first degree relatives’ of the affected patients have two to

three time more chances of developing the disease.[16-17] Identified causes of monogenic PD were thought to be remarkably uncommon until the discovey of LRRK2 i.e. 'leucine-rich repeat kinase' alterations[18] which induced upto 40% of cases in certain populaces.[19] Monogenic PD is widely assumed to be uncommon and is considered to be pertinent in as much as 5% of the overall PD cases; however a few argue that it might be associated with almost 5 to 10% of the cases.[20] Sporadic PD and Monogenic PD may vary clinically as well as pathologically with 'LRRK2' alteration being a special case which closely mimics sporadic PD. PD caused by mutation in 'SNCA' gene has an early emergence, a mild reaction to levodopa with a faster development; cognitive impairement, weakness and spasticity of extremities, psychotic conditions are also common. The cases involving recessive forms of PD normally appear at an early stage with onset of dyskinesia and have a decent response to levodopa with rare or no chances of cognitive impairement.[21] Besides monogenic PD, various genetic risk factors like 'α-synuclein variants', 'Heterozygous GBA mutations', 'Tau protein variants' have also been identified.[22-23] Smoking, consumption of alcohol, urate levels, vit. D exposure are some of the Environmental factors which may interact with unknown or known genetic factors to affect the disease's overall risk.[23] Yet, a few figures also suggest that impact of environmental factors might be of little significance.[24]

Diagnosis of PD

PD was initially viewed as an unadultered development issue with 'bradykinesia', 'tremors', and 'rigidity' as three major symptoms. Over time, instability and changes in posture have been exercised as a fourth major symptom.[25] However in nineties, only 80% of the PD cases satisfied the disease's criteria and a significant number of clinically diagnosed PD cases did not met the histopathological criteria.[26-27] As of late the clinical demonstrative standards of PD were reexamined[28] and 'rigidity', 'resting tremors' and 'bradykinesia' are still emphasized as key symptoms but, instability and changes in posture are excluded. 'Bradykinesia' is a required symptom that must occur in conjunction with 'resting tremors', 'rigidity', or even both. The detection of ''clinically established PD'' necessitates the presence at least 'two supportive criteria', 'the lack of absolute exclusion criteria', and 'absence of red flags'. The 'supportive criteria' involves 'presence of levodopa-initiated dyskinesia', 'asymmetric rest tremor', 'effect of dopaminergic therapy', 'positive tests on cardiac sympathetic denervation or olfactory loss'; covering both motor and non-motor signs and symptoms of PD. 'Supra nuclear gaze palsy', 'frontotemporal cognitive changes', 'cortical findings such as apraxia', 'slow progression', 'use of anti-dopaminergic therapy',

'normal DAT scan', 'lack of levodopa response', 'cerebellar abnormalities' are included in 'absolute exclusion criteria'. 'Red flags' comprise of 'inspiratory respiratory dysfunction', 'bilateral symmetric parkinsonism throughout the disease course' 'early gait impairment', 'recurrent falls due to reduced balance', 'early bulbar dysfunction', 'severe autonomic failure during the first year of the disease', 'absence of progression', 'early antecollis', 'pyramidal tract signs', and lack of any of the general NMS found in PD.

Pathophysiology

PD is pathologically defined as loss or degeneration of dopamine producing (DAnergic) neurons in substantia nigra region of the brain leading to significant dysfunction in motor control as well as formation of lewy bodies in these neurons.[29] These changes may occur two decades or more before obvious symptoms appear.[30] Variety of proteins like 'ubiquitin' or 'α-syn' present in lewy bodies causes neuron functioning impairement. Various researches suggest that environmental stress like use of drugs or exposure to toxins and ageing may promote neuropathology especially 'Inflammaging' which causes cellular senescence of the neurons in brain over a period of time.[31-32] Nearly 60 to 70% of the neurons in the 'substantia nigra pars compacta' disappear, once symptoms of PD appear.[33-34] Nerve cell death is caused by genetic mutations that code CNS proteins particularly α-syn which self-aggregates, turning into an abnormal, insoluble protein and is the chief component of 'cellular inclusions' and 'lewy bodies' all of which are sure signs of PD.[33] Other impaired processes like 'ubiquitin-proteasome' system (designed to breakdown abnormal proteins), 'mitochondrial dysfunction', or 'abnormal oxidative stress' (causes nerve cell degeneration through ROS) may play a role in PD.[33] Braak and colleagues theories[35] are used by some to elucidate pathophysiological development of PD.

Drug therapies for PD

Drug treatment is of the most popular approach in the management of PD with main goal being improving the quality of life of patients. Furthermore various therapies like physical therapy, occupational therapy, language therapy are also provided to the patients in an effort to facilitate patients to carry out various day to day activities independently for prolonged durations. Drug based treatment approaches are specially designed for a patient ensuring symptomatic relief while taking into account side effects and tolerance levels.[36]

Drugs used for the treatment of PD[36]

Class of Drug	Name of Drug	MOA
Dopamine agonist	Bromocriptine Pramipexole	Stimulates dopamine receptors directly
Combinations of L-dopa	L-dopa/Carbidopa	Metabolism of dopamine in cells containing dopa-decarboxylase
MAO inhibitors	Selegilline	Reduces dopamine metabolism by blocking MAO-B receptors
COMT inhibitors	Entacapone	Preserves catecholamine by blocking peripheral activity of COMT
Anticholinergic	Benzatropine Trihexyphenidyl	Prevents dopamine degeneration by blocking acetylcholine receptors

Physical therapy for PD

Beside drug therapies, patients suffering from PD are advised to undergo various trainings for strength, agility, balance, flexibility in order to improve non-motor symptoms and postural instabilities.[37] A latest systematic evaluation underlines the advantages of physical exercise programs (over a period of decade) involving activities like dancing, treadmill training, and exercising improved both motor and non-motor symptoms as well as cognitive functions in mild to severe patients and enhanced their quality of life.[38-41] Progress in talking with walking was noticed in patients after training hence enhancing balance, gait and cognition.[42] Music-based movement therapy also seems to be helpful for stride lengths.[43]

Strategies and future perspectives of PD

Ablative surgeries

Dating back to 1950s with an extensive record of clinical practices, Ablative surgeries were eventually phased out due to drug therapies. However these surgeries resurfaced in 1990s due to technological advancements, non-permanent therapeutic effects of drugs and related side effects.

Primarily, the removal of specific region of brain reduces symptoms of the disease and has no effects on bodily functions. Depending upon the symptoms involved, these surgeries can be done either unilaterally or bilaterally in the patient suffering from PD. Clinical benefits have been considered for surgical ablation of the thalamus (thalamotomy), globus pallidus internal (pallidotomy), and subthalamic (subthalamotomy) areas. Over a 7.9-year follow-up period, a study of approx. 200 patients with thalamotomy reported consistent improvements in 24.5 of patients and modest improvements in 45.2% of patients.[44]

Deep brain stimulation (DBS)

According to various researches, DBS appears to play a significant part in reducing motor symptoms of PD. Due to modern advancements in DBS technology and stereotactic methods, it is significantly considered for its uses in PD patients, thus vilifying ablative surgeries.[45] The procedure involves stereotactic approach where fine electrodes are placed in specific parts of basal ganglia like Globulus pallidus internal and Sub-thalamic nucleus with high frequencies stimulation. The device containing the battery is placed beneath the clavicle. PD patients with no major cognitive impairments and tolerance to medication side effects are suggested to undergo DBS installation. For optimal management of motor skills, precise supervision of DBS programming is preferred as surgery related infections are frequently reported. The applications of DBS are restricted to early to mild stages, cognitive impairments and associated symptoms.[46]

Gene editing CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-Cas9

It is a newly developed 'gene editing' technology to treat familial PD. CRISPR uses 'Cas9', a RNA-guided endonuclease, to cut dsDNA and allow editing in genes.[47] In order to edit the mutated genes, 'Cas9' creates double-stranded breaks at particular locations of DNA thus initiating the process of cellular repair. As a result, by using a stereotactic injection of an 'RNA-guided editing tool', genetic alteration in familial PD can be reversed.[48] This technique provides the opportunity to modify germ cell line DNA to eliminate familial PD in upcoming generations.[49] A recent study describes the use of fluorescent labeled markers for editing the mutated PD gene via 'fluorescence-activated cell sorting' (FAC)-assisted CRISPR/Cas9 editing to treat mutations linked to PD (A30P and A53T) of α-syn gene.[50]

New therapeutic targets

Ongoing information on the fundamental mechanism and physiopathology of Parkinson's disease may uphold the investigation to find new targets in order to cure this disease. The following are the most potential targets and systems to confine the deficiency of dopaminergic neurons.

Toxicity of α-syn (Alpha-synuclein)

α-syn is made up of 140 amino acids is the primary constituent of Lewy bodies and it is by all accounts firmly connected to PD pathogenesis.[51] Nonetheless, the job of α-syn on the beginning and development of PD isn't completely perceived. The main function of α-syn is

the assembly of a 'snare complex' by communicating with synaptic vesicles and thus controlling synapses.[52] Curiously, α-syn manifestation is expanded with increase in age.[53] The ramifications of α-syn in PD is due to the distinguishing proof of transformations in the SNCA gene in PD families. Duplicating or tripling of SNCA gene at 'PARK4 locus' has additionally been embroiled in this disease, showing that "α-syn-wild type" can cause toxicity at undeniable levels.[54] Moreover familial PD is linked to mutations at 'PARK1 locus' of SNCA gene influencing α-syn compliance, subsequently focusing on post-translational adjustments α-syn has additionally caught the attention of many and hence have centered their focus on α-syn for remedial mediation.

Proteasome and lysosome approach

Ubiquitin-proteasome mechanism and the autophagic-lysosomal processes are the two main debasement pathways for proteins including α-syn. The functioning and effectiveness of both these systems decrease with age. The proteasome enzyme first ubiquitinates and then degrades oligomeric and soluble forms of α-syn. In Parkinson's disease, intracellular inclusions can be result of malfunction of the 'ubiquitin proteasome system'. As a result, new drugs should be designed on the basis of proteasome system activators that can assist clearance of α-syn. The mutation in parkin gene has been linked to familial PD in this case, and malfunctioned proteins are labelled by ubiquitination for proteasome selective destruction.[55]

The growth of the aged pigment lipofuscin as a lysosomal degradation product of mitochondrial dysfunction demonstrates that macro autophagy is a neuroprotective mechanism during ageing.[21] Macro autophagy is a unique process that allows entire organelles, such as mitochondria, to be reused.[56] Prior to entering the lysosome, a specific cytosolic protein–atomic chaperone (hsc70) binds to the lysosomal associated membrane receptor protein 2 (LAMP2A), resulting in chaperone-mediated autophagy.[57] α-syn is an identified starting material of chaperone mediated autophagy and as of late announced that overexpression of α-syn is associated with reduction of LAMP-1, showing a decrease in phagocytic capacity and mitophagy disruption.[58] More examinations are expected to result in new molecules which will upgrade the lysosome-autophagy framework, thereby increasing α-syn breakdown.

Mitochondrial disruptions and oxidative stress

'Mitochondrial dysfunction' has been engaged with the etiology and pathogenesis of Parkinson's disease. As a result, treatments focusing on mitochondria that are coordinated to increase mitochondrial work have arisen as likely therapeutic targets for PD. Though PD is the result of many variables interacting, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and additional specific dopaminergic neurotoxins that repress 'mitochondrial complex' are currently utilized to make models supporting 'mitochondrial damage' in PD.[59] 'PTEN'- initiated 'putative kinase 1' (PINK1) and 'E3 ubiquitin protein ligase' (PARKIN) gene alterations include various proteins and processes identified with mitophagy of damaged mitochondria, fusion/fission and axonal transport[60] that have been linked to familial Parkinson's disease.

Mitochondria are notable wellspring of oxidative stress. Oxidative stress assumes a significant part both in PD and aging. As indicated by this, and significantly, DJ-1, a protein deglycase that protects against oxidative stressors, is faulty in both Parkinson's disease and ageing.[60] Aside from the fact that Reactive oxygen species (ROS) and free radicals such as H202 and OH- are formed in the mitochondria, some researchers believe that the nitrative and oxidative impairement of DAnergic cells can be connected to an increase in cytosolic dopaminergic metabolites.[53] The 'dopaminergic transporter' and the 'vesicular monoamine transporter 2' may have a protective function, in this case being responsible for the removal of excess free radical formation. In this regard, therapies involving replacement of antioxidants assume a significant part in the search for new and modern medications for neurodegenerative issues associated with ageing.

Glial environment and neuroinflammation

Cytosolic systems, as well as the nearby atmosphere of the dopaminergic nerve cells, have been considered to enhance the development of PD and also affecting the age factor. Microglia have been depicted to have affinity for macrophages, discharging neuroinflammatory cytokines and driving cell disintegration.[60] Neuroprotection is maintained by astrocytes (by overexpressing glial fibrillary acidic protein or altering their morphology). In any case, astrocyte initiation is considerd to be connected to a large part of the brain pathologies, counting Parkinson's. Focusing on the neuroinflammatory interaction might be an appropriate methodology to stop the development of this disease. Besides, anti-inflammatory drugs eg minocycline NSAIDS are also being examined at present as expected

neuroprotectants.[61] At long last, exenatide (a type 2 diabetes medication), the glucagon-like peptide 1 receptor agonist is also being studied in clinical trials in patients with PD.[62] The improvement of latest medications ought to be centered around initiating suitable neurotrophic and neuroprotective pathways so as to activate gliogenesis and neurogenesis.

CONCLUSION

PD is a degenerative disorder affecting CNS and causes various motor and non-motor impairments which limit the physiological freedom of the patients. The pathogenesis of PD actually stays indistinct and the molecular basis working in the mechanism of death of dopaminergic cells is obscure. Concerning existing PD treatments, the vast majority of them are pointed towards tending to motor symptoms, and yet there is no treatment centered around altering the course of illness. Along these lines, there is a dire exigency to create both disease-modifying and symptomatic treatments. However, extra research is needed before any of these promising techniques will open up in clinical work on carrying significant advantages to PD patients.

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