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Novel Therapeutic Technologies in Parkinsonism A Review

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ABSTRACT

Parkinsonism is one of the most common forms of neurodegenerative disease and is particularly associated with the loss of dopaminergic neurons within the substantia nigra. Parkinsonism, a group of chronic neurological disorders characterized by progressive loss of motor function resulting from the degeneration of neurons in the area of the brain that controls voluntary movement. [1] Various types of the disorder are recognized, but the disease described by Parkinson, called Parkinson disease, is the most common form. Parkinson disease is also called primary Parkinsonism, paralysis agitans, or idiopathic Parkinsonism. This distinguishes it from secondary Parkinsonism, a group of disorders very similar in nature to Parkinson disease but that arise from known or identifiable causes. The onset of Parkinson disease typically occurs between the ages of 60 and 70, although it can occur before the age of 40. It is rarely inherited. Parkinson disease often begins with a slight tremor of the thumb and forefinger, sometimes called "pill-rolling," and slowly progresses over 10 to 20 years, resulting in paralysis, dementia, and death. All types of Parkinsonism are characterized by four main signs, including tremors of resting muscles, particularly of the hands; muscular rigidity of the arms, legs, and neck; difficulty in initiating movement and postural instability. A variety of other features may accompany these characteristics, including a lack of facial expression (known as "masked face"), difficulty in swallowing or speaking, loss of balance, a shuffling gait, depression, and dementia.

KEYWORDS

Agitans, bradykinesia, dopamine, levodopa, Parkinsonian, putamen, shaking palsy,

INTRODUCTION

Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. The disease has a significant clinical impact on patients, families, and care- givers through its progressive degenerative effects on mobility and muscle control. The motor symptoms of PD are attributed to the loss of striatal dopaminergic neurons, although the presence of nonmotor symptoms supports neuronal loss in nondopaminergic areas as well. The term Parkinsonism is a symptom complex used to describe the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. PD is the most common cause of Parkinsonism, although a number of secondary causes also exist, including diseases that mimic PD and drug-induced causes. [2, 3]

HISTORY

Patients with PD usually complain of sleep abnormalities, reduced facial expressions, increased clumsiness on one side of the body, and a feeling of being persistently tired. PD usually

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demonstrates the presence of asymmetric rigidity and bradykinesia and resting tremors.

1) Rigidity: It is manifested as an increase in resistance when performing a passive movement. It is usually asymmetric. PD can have cogwheel rigidity, in which there is a ratchet-like movement at the beginning and end when a limb moves in a full range of motion. [4, 5] Patients complain of the stiffness of the limbs. "Cogwheeling" rigidity is the classic description of this rigidity.

2) Bradykinesia: Described as slowness of movement. Individuals may often complain of difficulty when carrying out simple, everyday tasks.[6] Mask-like facies where the face loses expression. Speech becomes soft and some patients have difficulty in speaking (dysarthria).

3) Tremor: The tremor seen in PD is characteristically the "pill-rolling tremor." It usually occurs when the individual is not involved in any activity, manifested at rest. [7] Tremor can also cause the involvement of lower limbs, lips, tongue but rarely manifests in the head. Stress worsens the tremor.

4) Postural Instability: An unstable posture results in an increased risk of falls due to the inability to balance. Walking is slow with a tendency to shuffle and decreased stride length.

ETIOLOGY

Parkinson's disease (PD) is the most common cause of Parkinsonism. It is a gradually progressive disorder that manifests as asymmetric Parkinsonism. There is dopaminergic neuronal loss in the midbrain due to neuronal degeneration, and these results in a decrease in dopamine levels, especially in the post-commissural putamen and other regions of the basal ganglia. PD typically responds to levodopa therapy. [8] Secondary causes of Parkinsonism typically do not respond to levodopa therapy.

Normal pressure Hydrocephalus (NPH)

It manifests with the classic triad of ataxia, urinary incontinence, and dementia. Parkinsonism may sometimes be the presenting symptom in NPH. [9] The earliest reporting of Parkinsonian features and hydrocephalus included the involvement of tumors of the posterior fossa. [10]

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Vascular Parkinsonism (VP)

Critchley was the first to describe VP as a separate entity in 1929. Previously, clinicians referred to VP as arteriosclerotic Parkinsonism, lower-body Parkinsonism, and vascular pseudo Parkinsonism. [11]

VP usually occurs due to an underlying vascular disorder, most commonly hypertension that leads to subcortical infarcts, white matter ischemia, and also large vessel infarcts. Diffuse white matter ischemic lesions present bilaterally can lead to the destruction of thalamocortical functioning reducing the impulses sent to the higher centers via the basal ganglia, result in disruption of motor movements. Imaging studies usually help to support the symptomatic diagnosis of VP. [12]

Drug induced Parkinsonism (DIP)

Medications that block the dopamine receptors and interrupt the transmission of dopamine are known to cause secondary Parkinsonism. The risk factors for the development of DIP include the route, potency, and dose of the drug administered. Individuals who are on medications administered via the intramuscular route or in the form of suppositories are more likely to develop DIP, especially at lower doses as compared to administration via the intravenous route. [13] At the same time, a drug with higher potency is more likely to cause DIP when compared to a drug with lower potency. Parkinsonism usually occurs at higher doses of medications, since dopamine receptor blockade occurs at higher doses. [14]

Toxin induced Parkinsonism (TIP)

Prolonged exposure to heavy metals and industrial toxins can result in Parkinsonian features. Toxins result in vast neurological damage resulting in Parkinsonism as compared to that seen in PD.

Brain Tumors

Several brain masses are responsible for the development of Parkinsonian features. These include meningioma, astrocytoma, craniopharyngioma, and sometimes even metastatic brain tumors.

Epidemiology Of Parkinson's Disease

Parkinson's disease (PD) affects 1-2 per 1000 of the population at any time. PD prevalence is increasing with age and PD affects 1% of the population above 60 years. It is more commonly seen in men as compared to women, with a male-to-female ratio of 1.5 to 1. [15]

PATHOPHYSIOLOGY OF PARKINSON'S DISEASE:

A decrease in the levels of dopamine that occurs relative to a degeneration of the substantia

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nigra results in decreased levels reaching the caudate and putamen; this leads to denervation hypersensitivity of dopamine receptors in those targets, especially of D1 and D2 receptors, within the nigrostriatal pathway. This yields increased inhibition in the thalamus, which subsequently causes a decrease in excitatory input to the motor cortex, which eventually manifests as bradykinesia and rigidity, seen in Parkinsonism presenting in PD.

In drug induced Parkinsonism, the dopamine D2 receptor which is present in the striatum is structurally or functionally blocked by the dopamine D2 receptor antagonists, causing a decrease in the dopamine levels, which results in similar dysfunction as seen in PD.

TREATMENT

Parkinson's disease can't be cured, but medications can help control the symptoms, often dramatically. In some cases, physical therapy that focuses on balance and stretching is important. A speech-language pathologist may help improve speech problems. Anti-Parkinsonian drugs are the mainstay symptomatic treatment for Parkinsonism, with different response intensity and duration for the different causes. The most responsive etiology is Parkinson's disease. [16]

MEDICATIONS

Medications may help manage problems with walking, movement and tremor. These medications increase or substitute for dopamine. People with Parkinson's disease have low brain dopamine concentrations. However, dopamine can't be given directly as it can't enter the brain. May have significant improvement of symptoms after beginning Parkinson's disease treatment. Over time, however, the benefits of drugs frequently diminish or become less consistent. Usually still control symptoms well.

Levodopa- Carbidopa

Dopamine itself cannot cross the blood-brain barrier. Levodopa, an amino acid gets metabolized to form dopamine, which compensates for the dopamine deficiency seen in PD. Furthermore, a peripheral dopa decarboxylase inhibitor, carbidopa is given along with levodopa for therapeutic advantage. Small doses of combined carbidopa-levodopa are given in a dose of 25/100 mg half tablet twice or thrice a day along with meals.

Dopamine agonists

These drugs stimulate dopamine receptors directly. The ergot derivative includes bromocriptine, and the non-ergot derivatives are ropinirole and pramipexole. Both these drugs are immediate release formulations that can be given three times daily. Pramipexole dosing is 0.125 mg three times a day whereas ropinirole is given as 0.25 mg thrice a day.

Catechol-O-methyltransferase (COMT) Inhibitors

Entacapone results in the blockade of peripheral COMT, an enzyme responsible for the degradation of dopamine. It helps to decrease the breakdown of levodopa, thus increasing its availability to the brain. Entacapone dosing is 200mg with every dose of levodopa, and up to eight doses can be given each day, whereas the dose of tolcapone is 100 mg three times a day.

Mono amine oxydase (MAO) inhibitors

Drugs like selegiline and rasagiline decrease the metabolism of dopamine by blocking the enzyme, monoamine oxidase. The daily dosing of selegiline is 5 mg, usually given in the morning to avoid insomnia. A dose greater than 10 mg should not be used in PD patients as it can lead to nonselective MAO inhibition causing a hypertensive crisis as a result of interaction with tyramine-containing foodstuff. Rasagiline can be initiated with a dose of 0.5 mg once a day and gradually increased to 1 mg once a day.

Amantadine

It acts by blocking N-methyl-D-aspartate and acetylcholine receptors. It is available as immediate-release tablets or capsules 100 mg each given twice or thrice daily. It is excreted via the kidney and thus should be used cautiously in patients with kidney injury.

Novel Approaches towards Parkinson Disease

In recent years, there has been a growing interest in the development of nanotechnologies for the treatment of PD. The delivery of nanoencapsulated drugs is a useful strategy to improve the efficacy of many macromolecules targeting the brain. NPs can increase the stability and bioavailability of dopamine, allowing the sustained release of dopamine and preventing its peripheral metabolism. [17]

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Gene therapies

Gene therapy is a rapid evolving, genome editing technology aiming to treat a disease by genetically modifying populations of cells that are either directly functionally impaired or capable of relieving disease symptoms.[18] The technology is based on the use of a vector to carry DNA, RNA, antisense oligonucleotides or DNA- or RNA-editing enzymes into specifc cells to modulate gene expression.[19] Increasing clinical evidence of viral vector-based gene therapy approaches is available in PD . As a result of studies on animal models that provided proof for the safety and eficacy of two families of viral vectors, characterized by both durable gene expression in neurons and minimal immunogenicity: adeno-associated viruses (AAVs) and lentiviruses (LVs). AAVs have been widely used as vectors in central nervous system (CNS) disorders.[20] The AAV serotype 2 (AAV2) has demonstrated excellent tropism for neurons , while other AAV serotypes have been used for targeting other cell populations in the CNS, such as astrocytes and microglia. Also, AAV2 vectors are characterized by limited risk of insertional mutagenesis for the host and efective expression after one-time delivery treatment.[21,22]

Gene therapy clinical trials in PD have focused on 4 main targeted approaches: (1) restoring dopamine synthesis, (2) neuroprotection, (3) genetic neuromodulation and (4) addressing disease-specifc pathogenic variants. Gene therapies targeting pathogenic GBA variants are addressed in the section "Glucocerebrosidase targeting therapies". [23]

PD trials focusing on dopamine restoration strategies have targeted either aromatic L-amino acid decarboxylase (AADC) alone using AAV2 as vectors (AAV2-AADC) or a triad of key enzymes in the dopamine biosynthetic pathway including AADC, tyrosine hydroxylase (TH) and GTP-cyclohydrolase (GCH1) using lentivectors (LV-GCH1-TH-AADC; ProSavin→).[24] AAV-AADC phase-I clinical trials demonstrated safety and a signifcant improvement of both motor and nonmotor symptoms as assessed by the Unifed Parkinson Disease Rating Scale (UPDRS), a decrease in OFF-time duration without an increased effect of ON-time dyskinesias, as well as an increase in the uptake of the AADC tracer at PET, which was used as a measure of gene expression.[25] A phase-Ib study demonstrated a dose-dependent improvement of clinical outcomes, including increase in ON-time duration without dyskinesias.

Thus, in clinical trials of gene therapies, outcome measures comprise both clinical improvement and functional neuroimaging markers of pharmacodynamics (e.g. dopaminergic neuron density and AADC activity) Also, in an attempt to closer explore drug effect on brain connectivity, consecutive FDG-PET scans were successfully combined with network analysis to provide insight in the metabolic signature of gene therapy, suggesting a new tool for the evaluation of therapeutic efficacy in PD

Nano-enabled gene delivery for the treatment of Parkinson's disease

In vivo gene transfer using viral vectors is a powerful strategy to overcome the limitation of BBB for the treatment of PD. Gene therapy for Parkinson's disease has entered clinical trials and is now in Phase 1 studies for which interim data has been accumulated. After numerous challenges, researchers have discovered that gene therapy for PD may be a reality. [26] In some ways, neurological gene therapy is in a similar stage to therapeutic monoclonal antibodies more than a decade ago. Delivery with nanotechnology appears to be an answer to this challenge. A study is underway examining a relatively new gene therapy approach for treating sexually transmitted diseases. Researchers are evaluating the feasibility of using nanotechnology to condense DNA plasmids into nanoparticles and deliver them to the brain as a means of stopping or preventing the neurodegenerative process.

Nanorobots as stem cell therapy for Parkinson's disease

The potential of cell therapy for Newcastle disease has been demonstrated in the implantation of different types of stem cells in animal models with PD. Rat brain stem cell transplantation demonstrated reinnervation of striatal neurons and partial recovery from the motor deficit associated with dopamine deficiency. Similar results were obtained after fetal dopaminergic neuron transplantation in clinical trials. So; various types of stem cells can be used to generate dopaminergic neurons. Currently, the process of differentiation of dopaminergic neurons from embryonic stem cells in vitro is more efficient.[27] Recent advances in human therapeutic cloning make this approach to neuron generation more attractive differentiation of embryonic stem cells in vitro and transplantation of dopaminergic neurons into animal models of PD have led to functional integration of the implanted cells in the receptor brain and recovery partial motor function.[28] Although neuronal transplantation in

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the striatum in the PD model is more efficient than neuronal transplantation in other DNs, the complete restoration of the motor deficit associated with PD is still far from its goal. In the case of PD, significant functional recovery requires cell replacement with at least partial repair of the original connections with neurons in the striatum. If no such connections exist, complete regression of the motor deficit is impossible since dopamine release is under a feedback control mechanism. This fact underlines the importance of developing effective methods to stimulate axon growth in the wrong directions. [29] After transplantation, stem cells make decisions about fate and patterns in response to external signals from the extracellular environment and neighboring cells. The efficacy of neural stem cell therapy can be facilitated by the ability to manipulate these signals in an appropriate temporal and spatial manner. [30]

Nano-enabled immune-liposomes for gene replacement therapy in Parkinson's disease

Macrophages, microglia and astrocytes readily absorb liposomes in the central nervous system. Pegylated liposomes accumulate more rapidly in the brain when BBB is impaired, as in experimental autoimmune encephalomyelitis. [31] Furthermore, PEGylated immunoliposomes containing antibodies directed against insulin or transferrin receptors have been successfully used as vehicles for gene replacement therapy in the PD model. The mechanism by which immune liposomes pass through the BBB is not fully understood. It has been hypothesized that it involves binding of immunoliposomes to receptors on the luminal membrane of capillaries, fusion of liposomes with several vesicular holes in a large vesicle, and transcytosis of this vesicle at the edge of the abluminal membrane. In terms of liposome targeting, PEGylated immunoliposomes have been used to target and temporarily transfect galactosidase (LacZ reporter gene) and luciferase in the brain.[32] The gene was incorporated into the center of the liposome, which was then coated with PEG to prolong circulation time by reducing the absorption of liposomes by the RES. Furthermore, another 2% of the PEG chains have a transferrin receptor mAb (mAb 8D3) attached to them. MAb then interacts with transfer receptors and, in effect, directs the immunoliposome to tissues that have a high expression of transferrin receptors, such as the brain. Furthermore, encapsulation of a specific brain promoter (eg glial fibrillar acid protein, GFAP) with the β-galactosidase gene has been shown to restrict enzyme expression in the brain.

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