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Nanoparticle- Drug Delivery Systems for Parkinson's Disease

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Abstract

Parkinson's disease is a complex neurological condition. It has long been recognized by the loss of dopaminergic neurons in the substantia nigra and the characteristic motor symptoms of parkinsonism associated with Lewy bodies. But Parkinson's disease symptomatology is now understood to be diverse, including clinically significant non-motor characteristics. Similar to Lewy bodies, its disease encompasses numerous areas of the nervous system, numerous neurotransmitters, and other protein aggregates. Although the exact etiology of Parkinson's disease is still unknown, environmental factors are no longer thought to be the main cause of the condition. Instead, a complex interplay of hereditary and environmental factors that alter a number of essential cellular processes appears to be the cause of Parkinson's disease. Clinical issues that come with Parkinson's disease's complexity include the inability to make a conclusive diagnosis in the disease's early stages and challenges managing symptoms in the disease's later stages. In addition, there is no medicine that can stop the neurodegenerative process. We go over the complications and difficulties of Parkinson's illness in this seminar.

Key Words: Parkinson's disease, symptom, tremors

Introduction

James Parkinson first described the clinical condition now known as Parkinson's disease (PD) in 1817 in his famous publication *"*An Essay on the Shaking Palsy." Parkinson's disease is primarily characterized by major motor symptoms such as resting tremor, bradykinesia (slowness of movement), muscular rigidity, and impairment of postural balance. In addition to these hallmark motor features; patients often experience several other motor and non-motor symptoms that contribute significantly to disease burden (1–3).

Among the various non-motor symptoms, autonomic dysfunction is considered an important clinical manifestation associated with Parkinson's disease (4). In recent years, considerable research attention has been directed toward understanding the role of autonomic dysfunction in the early detection and prediction of PD (4–5).

As global life expectancy continues to rise, age-related disorders such as Parkinson's disease are gaining

increasing attention within the scientific and medical communities. Currently, PD is recognized as one of the fastest-growing neurological disorders worldwide and is a major contributor to disability among the aging population (6).

Although the exact mechanisms responsible for autonomic failure in Parkinson's disease remain unclear, several pathological findings have demonstrated the presence of α-synuclein accumulation along with degeneration of autonomic nerves within different components of the autonomic nervous system. These include the peripheral sympathetic, parasympathetic, and enteric nervous systems (7–8).

While autonomic dysfunction may not occur in every case of Parkinson's disease, growing evidence suggests that it may contribute to the underlying pathogenesis of the disorder. Traditionally, most cases of PD have been described as idiopathic, meaning that the exact cause is unknown. However, advances in research have identified monogenic forms of Parkinson's disease that may present clinically similar to idiopathic PD. Furthermore, the classification of PD continues to evolve due to the considerable clinical heterogeneity of the disease and the overlapping features it shares with other neurodegenerative conditions such as PD-related dementia, dementia with Lewy bodies, and other parkinsonian syndromes.

To facilitate better assessment of autonomic disturbances in PD patients, the International Parkinson and Movement Disorder Society (MDS) has recommended the use of several standardized clinical rating scales. (9–11).

Epidemiology

Patients suffering from Parkinson's disease (PD) often experience symptoms related to autonomic dysfunction that can affect several physiological systems. These dysautonomic manifestations generally occur in at least four major functional domains, including disturbances in the pupillo-motor system, urinary function, sexual function, and thermoregulation. In addition to these symptoms, individuals with PD may also show abnormalities in pupillary response and tear secretion. These changes are mainly associated with the progressive degeneration of autonomic nerve fibers that regulate ocular functions.

To emphasize the importance of understanding autonomic involvement in Parkinson's disease, this section presents the epidemiological aspects of dysautonomic symptoms observed in PD patients. Studying their prevalence and distribution helps highlight the clinical significance of autonomic dysfunction and the need for further investigation into its role in the progression and management of Parkinson's disease.

Gastrointestinal Dysfunction

Gastrointestinal disturbances are commonly observed in individuals with Parkinson's disease (PD), and these symptoms may appear even before the typical motor signs of the disease become evident. In many cases, such digestive problems occur during the premotor or prodromal phase of Parkinson's disease. Research findings indicate that approximately 88.9% of individuals with PD report gastrointestinal symptoms prior to the onset of characteristic parkinsonian motor manifestations (12). These observations suggest that

gastrointestinal dysfunction may serve as an early clinical indicator of the disease.

Weight Loss

Approximately half of individuals diagnosed with Parkinson's disease (PD) experience weight loss as the disease progresses. Several factors may contribute to this reduction in body weight, including tremor, muscle rigidity, and the use of medications such as levodopa (13).

For a more accurate understanding of weight loss directly related to disease progression, it is preferable to evaluate patients at the time of initial diagnosis, before pharmacological treatment begins. However, due to limited research attention, the exact prevalence of weight loss during the premotor or pre-diagnostic phase of Parkinson's disease remains uncertain.

Sialorrhea

Sialorrhea, commonly referred to as excessive drooling, occurs in nearly 50% of patients in the early stages of PD (14). This condition can lead to drooling during both daytime and nighttime.

The prevalence of drooling in PD patients ranges from approximately 32% to 74%, while a comprehensive analysis estimated the overall prevalence to be around 56% (15). Persistent drooling is reported in about one-quarter of individuals with Parkinson's disease, and more than 20% experience drooling specifically during daytime. This condition presents a major therapeutic challenge because it may cause social embarrassment and significantly increase the risk of aspiration pneumonia.

Dysphagia

Difficulty in swallowing, known as dysphagia, is another common gastrointestinal complication observed in PD. A systematic review reported that dysphagia affects between 11% and 81% of patients with Parkinson's disease (16).

More than 15% of individuals newly diagnosed with PD may develop swallowing difficulties. Both the prevalence and severity of dysphagia tend to increase as the disease advances (17).

Research suggests that factors such as sex, age, duration of the disease, and the presence of dementia may independently influence the likelihood of swallowing impairment. Dysphagia can significantly reduce quality of life and is considered an indicator of poor prognosis in the later stages of Parkinson's disease.

Gastroparesis

The exact prevalence of gastroparesis in Parkinson's disease has not yet been clearly established. However, PD accounts for approximately 7.5% of gastroparesis cases among the known causes (18).

Studies have reported that delayed gastric emptying may occur in 70% to 100% of PD patients, although

many individuals remain asymptomatic. Gastroparesis can occur even during the premotor phase of the disease, although its frequency does not appear significantly higher than that observed in the general population (19).

This condition can negatively affect nutritional intake and overall health. Furthermore, delayed gastric emptying may postpone the peak plasma concentration of levodopa, potentially affecting the effectiveness of treatment in Parkinson's disease.

Small Intestinal Bacterial Overgrowth Syndrome

Small intestinal bacterial overgrowth (SIBO) refers to the presence of excessive bacterial populations within the small intestine. Among individuals with PD, the prevalence of SIBO is estimated to range between 20% and 60%.

SIBO represents an important concern in the management of Parkinson's disease because it may worsen gastrointestinal symptoms and can also aggravate motor dysfunction.

Cardiovascular Dysfunction

Orthostatic Hypotension

Orthostatic hypotension (OH) is one of the most frequently observed cardiovascular manifestations in Parkinson's disease. A large meta-analysis estimated the prevalence of OH in PD to be around 30%, with approximately 40% occurring in early-stage patients (20).

Another clinical study identified orthostatic hypotension even in individuals with PD who had not yet received pharmacological treatment (21).

Therefore, OH can occur even in the early stages of Parkinson's disease. This condition may significantly affect the progression of the disease and reduce quality of life, as it increases the need for medical care, impairs cognitive performance, interferes with daily activities, and raises the risk of falls requiring medical attention. Patients with OH often exhibit more severe motor impairments, and even asymptomatic OH may hinder routine daily tasks.

Postprandial Hypotension

Postprandial hypotension, defined as a drop in blood pressure after meals, is another cardiovascular feature commonly observed in early Parkinson's disease, with a prevalence exceeding 30% (22).

A recent systematic review and meta-analysis reported that individuals with PD have an odds ratio of 3.49 for developing postprandial hypotension compared to the general population (23).

The condition is more common in patients who already have orthostatic hypotension. Among elderly

individuals receiving low-level care, postprandial hypotension has been associated with worsening parkinsonian motor symptoms and may serve as a predictor of all-cause mortality (22).

Nondipping

Nondipping refers to the absence or reduction of the normal decrease in blood pressure during nighttime sleep (24).

Only a limited number of studies have investigated this phenomenon in Parkinson's disease. However, nondipping appears to be more common in PD patients who also have orthostatic hypotension than in those without it (24–25).

One study reported that approximately 88% of individuals with PD exhibit nondipping patterns. Another recent investigation found that more than 80% of PD patients demonstrate abnormal dipping patterns (26). Additionally, reverse dipping—where blood pressure increases during the night—has been proposed as a biomarker of autonomic dysfunction in Parkinson's disease, indicating abnormal regulation of nocturnal blood pressure (27).

Supine Hypertension

Supine hypertension is another cardiovascular abnormality frequently associated with orthostatic hypotension and autonomic dysfunction (28).

Approximately 34% of PD patients experience supine hypertension. This condition has been linked with greater reductions in systolic and diastolic blood pressure during orthostatic changes, as well as an increased risk of cardiovascular complications and cognitive impairment (29).

Supine hypertension may also elevate the likelihood of conditions such as dementia and stroke.

Urogenital Dysfunction

Urinary Dysfunction

Urinary disturbances are widely reported in individuals with Parkinson's disease. Previous studies have indicated that between 27% and 85% of PD patients experience urinary problems, with most symptoms belonging to the irritative category (30–31).

It is estimated that nearly 64% of individuals with PD develop urinary symptoms (32). Urinary difficulties often appear in the early stages of the disease. Nocturia is the most frequently reported symptom, followed by urinary frequency and incontinence. Approximately one-quarter of affected patients also develop functional obstructive urinary symptoms (33).

Sexual Dysfunction

Sexual dysfunction is reported in more than half of individuals with early-stage Parkinson's disease. In some

cases, dopamine replacement therapy may lead to hypersexuality or abnormal sexual behaviour due to impaired impulse control rather than autonomic dysfunction itself (14).

Reduced libido and decreased sexual arousal are common symptoms affecting both male and female patients (34–35).

Male patients frequently experience erectile dysfunction, hypersexuality, or abnormal ejaculation, whereas female patients may develop reduced vaginal lubrication and involuntary urination during sexual activity. These problems can significantly affect emotional health and overall quality of life.

Thermoregulatory Dysfunction

Hyperhidrosis, particularly excessive sweating during the night, is one of the most common manifestations of thermoregulatory dysfunction in Parkinson's disease (36–37).

Patients who experience hyperhidrosis often show a higher burden of autonomic dysfunction compared to those without this symptom. They may also exhibit increased dyskinesia, reduced quality of life, and greater levels of psychological stress and depression (37).

Pupillo-Motor and Tear Abnormalities

It has long been recognized that Parkinson's disease can affect the pupillary light reflex. Disturbances in pupillary function have also been associated with both motor and non-motor symptoms of the disease (38).

Studies have shown that individuals with PD demonstrate increased pupillary sensitivity to both sympathomimetic and parasympathomimetic drugs (39).

Impaired tear production in PD patients was first reported in 2005 . However, the precise clinical significance of pupillary and tear abnormalities in Parkinson's disease remains unclear.

Fig no.1 -Symptoms of Parkinson's Disease

Pathogenesis

Neuropathology

In Parkinson's disease (PD), autonomic neuropathology is mainly characterized by two key features: degeneration of autonomic neurons and abnormal accumulation of α-synuclein. Neuronal degeneration involves the progressive loss of neurons, deterioration of nerve fibres, and reduction of synaptic connections. The presence of Lewy bodies represents the abnormal intracellular accumulation of α-synuclein protein. Both neuronal loss and α-synuclein deposition have been identified in several regions that play an essential role in autonomic regulation. These central autonomic control areas include the cerebral cortex, insular cortex, hypothalamus, brainstem, and spinal cord (39).

In addition to the central nervous system, pathological changes are also observed in components of the peripheral autonomic nervous system. Structures such as the vagus nerve, sympathetic nerve fibres, and the enteric nervous system frequently demonstrate

neuronal degeneration along with α-synuclein pathology. In many cases, these peripheral abnormalities may appear earlier than the neuropathological changes observed in the central nervous system.

Experimental studies using animal models of Parkinson's disease have also reproduced similar pathological alterations within the autonomic nervous system. These models demonstrate both α-synuclein aggregation and neuronal degeneration. For example, prolonged administration of rotenone in experimental models has been shown to significantly increase α-synuclein aggregation in the intestine, forming structures similar to the Lewy bodies observed in idiopathic PD patients (40-39).

Genetic Factors

Genetic influences play an important role in determining various clinical manifestations of Parkinson's disease, including both motor and non-motor symptoms. Several studies have suggested that genetic variations may also contribute to autonomic dysfunction in PD.

Certain gene mutations associated with familial forms of Parkinson's disease have been linked to disturbances in autonomic function. In many cases, autonomic symptoms may appear during the early stages of familial PD and may even be present during the premotor phase of the disease (41).

Research findings indicate that cardiac sympathetic denervation in PD is associated with duplication or triplication of the SNCA gene. Furthermore, cardiac sympathetic denervation has been reported not only in symptomatic individuals but also in asymptomatic carriers of the SNCA E46K mutation, suggesting that genetic alterations may contribute to autonomic nervous system involvement even before clinical symptoms become evident.

Contrarily, in familial PD patients with PARK2 (parkin RING-Between-RING E3 ubiquitin protein ligase) and PARK9 (ATPase Cation Transporting 13A2) mutations, autonomic dysfunction is less common and severe during the course of the illness s. According to past research, those who carry the LRRK2 mutation typically had greater cardiac MIBG uptake, less gastrointestinal dysfunction, and less intact heart rate variability (HRV) than non-carriers, people with idiopathic PD . But according to recent research, LRRK2

G2019S mutation carriers had enhanced beat-to-beat HRV, while LRRK2 R1441G mutation carriers had higher dysautonomia ratings than noncarriers (41).

Environmental Factors

Only a limited number of studies have explored how environmental factors contribute to autonomic dysfunction associated with Parkinson's disease (PD) and to pathological changes resembling those seen in the disorder. Exposure to environmental contaminants and toxins may influence biological processes and potentially play a role in the development or progression of PD-related abnormalities.

The gastrointestinal tract serves as a major interface between the external environment and the body's internal physiological system. Because of this close interaction, the digestive system is particularly susceptible to environmental influences. Increasing evidence suggests that alterations in gut microbiota composition play an important role in the pathophysiology of Parkinson's disease. Such microbial changes may contribute to inflammatory responses, neuronal damage, and other biological mechanisms involved in the onset and progression of the disease. Studies using 16S ribosomal RNA gene amplicon sequencing have demonstrated that individuals with PD often exhibit an imbalance in their gut microbial population (42).

Intestinal dysfunction in PD may also be associated with small intestinal bacterial overgrowth (SIBO), which is considered one of the most frequently observed gastrointestinal manifestations of the disease. However, current findings suggest that SIBO may represent a parallel outcome rather than a direct cause of gastrointestinal disturbances, as its presence does not appear to correlate with more severe gastrointestinal symptoms in PD patients.

Furthermore, disturbances in gut microbiota composition, commonly referred to as dysbiosis, have been linked to abnormalities in bile acid metabolism and changes in lipid metabolism in PD. These findings suggest that alterations in the gut microbial environment may influence biochemical metabolic processes within the intestine, thereby contributing to gastrointestinal dysfunction in Parkinson's disease.

Another question that remains unresolved is whether autonomic dysfunction in PD is associated with gastrointestinal infections. Research indicates that infection with Helicobacter pylori (HP) occurs in approximately one-third of individuals with Parkinson's disease. Although HP-positive patients have been reported to exhibit poorer motor performance, studies have found that gastrointestinal symptoms are not significantly affected by the presence of this infection (43).

Recent experimental studies have also shown that infections caused by intestinal Gram-negative bacteria may trigger mitochondrial antigen presentation and the activation of cytotoxic mitochondria-specific $CD8^+$ T lymphocytes in both the brain and peripheral tissues in Pink1-/- mouse models. These findings suggest that autoimmune and inflammatory mechanisms may play a role in linking intestinal dysfunction with autonomic disturbances in Parkinson's disease (44).

Nanotherapeutics-Mediated Intranasal Delivery for Therapeutic Effect on Parkinson's Disease

Nanoparticle Drug Delivery Systems (NDDS) are emerging as advanced strategies to overcome major therapeutic challenges in Parkinson's disease (PD) by improving drug delivery efficiency, targeting capability, and overall therapeutic outcomes.

One of the major challenges in the treatment of Parkinson's disease (PD) is the presence of the Blood–Brain Barrier (BBB). This highly selective physiological barrier tightly regulates the movement of substances between the bloodstream and the central nervous system, thereby limiting the ability of many therapeutic drugs to reach the brain effectively (45)

Conventional anti-parkinsonian therapies often exhibit poor BBB permeability, rapid systemic degradation, and limited brain bioavailability, resulting in reduced efficacy and increased peripheral side effects

Nanoparticle-based drug delivery systems offer a promising solution to these limitations, as they can be precisely engineered with optimized particle size, surface charge, and composition to facilitate BBB penetration. Nanoparticles may cross the BBB via receptor-mediated transcytosis by targeting endothelial receptors such as transferrin or insulin receptors, or through adsorptive-mediated transcytosis using positively charged surfaces

In addition, nanoparticles can bypass the BBB entirely through direct nose-to-brain delivery via the olfactory and trigeminal nerve pathways, providing a highly efficient route for brain targeting.

Beyond enhanced BBB transport, nanoparticles protect encapsulated drugs from enzymatic and chemical degradation, improve brain uptake, and allow controlled and sustained drug release, thereby maintaining therapeutic drug concentrations in the brain for extended durations and reducing dosing frequency (46).

Furthermore, surface-functionalized nanoparticles enable targeted delivery to dopaminergic neurons, minimizing off-target effects and enhancing therapeutic efficacy in PD.

Example: Dopamine-loaded nanoparticles for Parkinson's disease Bioinspired polymeric nanoparticles have been developed to encapsulate dopamine, overcoming its inherent inability to cross the BBB.

These dopamine-loaded nanoscale coordination polymers demonstrated high drug loading efficiency, low cytotoxicity, enhanced brain uptake, and improved therapeutic efficacy. Intranasal administration significantly increased striatal dopamine levels and improved motor function in Parkinson's disease animal models, highlighting the potential of nanoparticle-based dopamine replacement therapy (47).

Intranasal drug delivery has emerged as a particularly promising approach for the treatment of neurological disorders such as Parkinson's disease, as it enables non-invasive and direct transport of therapeutic agents to the brain while bypassing the BBB (48).

Drugs administered via the nasal cavity can reach the central nervous system through the olfactory and trigeminal nerve pathways, providing direct access to key brain regions involved in PD pathology, including the striatum and substantia nigra (49).

This route enhances brain drug concentration while minimizing systemic exposure, thereby reducing peripheral side effects such as gastrointestinal and cardiovascular complications commonly associated with oral or parenteral therapies (50).

Additionally, intranasal delivery avoids hepatic first-pass metabolism, resulting in improved bioavailability and rapid onset of action**.** When combined with nanoparticle-based formulations, intranasal administration further improves drug stability, prolongs residence time in the nasal mucosa, facilitates sustained drug release, and enhances neuronal uptake.

Overall, intranasal nanoparticle-mediated drug delivery represents a safe, patient-friendly, and highly effective strategy for targeted brain delivery, offering substantial advantages for long-term management of Parkinson's disease .

Example: Intranasal exosome-based nanocarrier for Parkinson's disease A self-oriented nanocarrier (PR-EXO/PP@Cur) combining mesenchymal stem cell-derived exosomes with curcumin has been developed for intranasal delivery in Parkinson's disease (51).

This system efficiently crossed multiple biological barriers and released therapeutic agents directly into neuronal cells, leading to reduced α-synuclein aggregation, suppression of neuroinflammation, and restoration of neuronal function. Intranasal administration of PR-EXO/PP@Cur significantly improved motor coordination and behavioural performance in Parkinson's disease model mice, highlighting its potential as an advanced brain-targeted nanotherapeutic strategy (52-54).

Functional Goals of Nanoparticle Drug Delivery Systems in Parkinson's Disease

1. Improved Pharmacokinetics

Nanoparticle-based delivery systems enhance the pharmacokinetic profile of anti-parkinsonian drugs by protecting them from premature enzymatic degradation and rapid systemic clearance (54). Encapsulation allows controlled and sustained drug release, maintaining optimal therapeutic concentrations in the brain for longer durations and reducing dosing frequency.

2. Neuroprotection

Nanoparticles can deliver neuroprotective agents such as antioxidants, anti-inflammatory drugs, neurotrophic factors, and mitochondrial-protective compounds directly to the brain. These agents help reduce oxidative stress and neuroinflammation, two major contributors to dopaminergic neuronal loss, thereby slowing disease

progression in Parkinson's disease (55).

3. Targeting Disease-Specific Pathways

Nanoparticles can be engineered to selectively target key pathological mechanisms involved in Parkinson's disease, including α-synuclein aggregation, mitochondrial dysfunction, oxidative damage, and chronic neuroinflammation. Targeted delivery improves therapeutic efficacy while minimizing off-target effects (56).

4. Enhanced Brain Targeting and Bioavailability

Surface modification of nanoparticles enables improved crossing of the blood–brain barrier and increased accumulation in affected brain regions such as the striatum and substantia nigra, resulting in enhanced bioavailability and reduced peripheral toxicity.

5. Reduced Systemic Side Effects

By localizing drug action within the central nervous system, nanoparticle systems limit unwanted peripheral exposure, thereby minimizing systemic adverse effects associated with conventional Parkinson's disease therapies.

Types of Nanoparticle Drug Delivery Systems Used in Parkinson's Disease Various nanoparticle-based drug delivery systems have been explored for the treatment of Parkinson's disease to overcome the limitations of conventional therapies (57). These nanocarriers differ in composition, structure, and drug-loading mechanisms, allowing tailored delivery of therapeutic agents to the brain. The most commonly investigated nanoparticle systems include-

- polymeric nanoparticles
- lipid-based nanoparticles
- inorganic nanoparticles
- biological nanocarriers such as exosomes

Polymeric nanoparticles are widely applied in drug delivery systems because of their advantageous characteristics. These nanoparticles are generally prepared using biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone. Their excellent biocompatibility, ability to provide controlled and sustained drug release, and the flexibility for surface modification make them suitable for various therapeutic applications (58).

These nanoparticle systems have also been effectively used for the delivery of therapeutic agents such as dopamine, levodopa, antioxidants, and other neuroprotective compounds. Their use has been shown to enhance drug bioavailability in the brain and provide prolonged therapeutic effects, which is particularly

beneficial in the management of Parkinson's disease (59).

Lipid-based nanoparticles, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are widely used in drug delivery because of their beneficial characteristics. These nanocarriers provide high drug-loading capacity, improved stability, and strong compatibility with lipophilic drugs (60). Moreover, these systems enhance the ability of therapeutic agents to cross the Blood–Brain Barrier, which is a major challenge in the treatment of Parkinson's disease. Studies conducted using Parkinson's disease models have shown that lipid-based nanoparticles can reduce systemic toxicity while improving overall therapeutic effectiveness.

Inorganic nanoparticles, such as gold, silica, and iron oxide nanoparticles, possess unique physicochemical properties including magnetic responsiveness and imaging capability. These nanoparticles have been explored for targeted drug delivery, diagnostic imaging, and theranostic applications in Parkinson's disease, although concerns regarding long-term toxicity remain (61).

Exosome-based nanocarriers, derived from biological sources such as mesenchymal stem cells, represent an emerging and highly promising delivery platform (62). Due to their inherent ability to cross biological barriers and low immunogenicity, exosomes can efficiently deliver neuroprotective agents, small molecules, and nucleic acids directly to neuronal cells. Exosome-mediated delivery systems have demonstrated significant improvements in motor function and neuroprotection in Parkinson's disease animal models.

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