RESEARCH PAPER

Late-Onset Parkinson's Disease with Atypical Tremor and Early Cognitive Dysfunction: Implications for Levodopa Pharmacokinetics and Emerging Drug Delivery Systems

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ABSTRACT

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in dopamine deficiency in the basal ganglia. Classical motor symptoms include resting tremor, bradykinesia, rigidity, and postural instability. However, substantial clinical heterogeneity exists, particularly in late-onset cases (>70 years), which may feature atypical tremor morphology and early cognitive impairment. Levodopa remains the cornerstone therapy but is limited by variable gastrointestinal absorption due to delayed gastric emptying, dietary amino-acid competition, and gut microbial metabolism.

Case Presentation: We report a 79-year-old man with late-onset parkinsonism presenting with asymmetrical high-frequency large-amplitude resting tremor, bradykinesia, shuffling gait, and executive cognitive dysfunction within 1 year of motor onset. Secondary causes were excluded by normal MRI and laboratory investigations. Diagnosis of idiopathic PD with atypical features was confirmed after excluding progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). Levodopa–carbidopa (Syndopa) was initiated with structured dosing, 2-hour meal–drug separation, and tablet dissolution in lemon juice to enhance gastric dissolution and absorption.

Conclusion: Moderate improvement in tremor and gait was achieved with pharmacokinetic optimization, though the response remained suboptimal compared with classical PD. This case highlights phenotypic variability in late-onset PD and the value of simple bedside strategies. Emerging intranasal and nanoparticle-based drug delivery systems offer promise for stable dopaminergic stimulation in atypical presentations.

Novelty: This case is unique in demonstrating the coexistence of atypical high-frequency large-amplitude tremor and early executive cognitive dysfunction in confirmed late-onset idiopathic Parkinson's disease, along with real-time clinical improvement using simple pharmacokinetic optimization strategies (acidic dissolution with lemon juice and strict meal–drug separation), which are rarely emphasized together in routine clinical reporting.

Keywords: Parkinson's disease; late-onset parkinsonism; atypical tremor; levodopa pharmacokinetics; drug delivery optimization; novel drug delivery systems

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Background

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1–2% of individuals over 65 years[1]. It arises from progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to motor symptoms (resting tremor, bradykinesia, rigidity, postural instability) and non-motor features including cognitive impairment[2].

PD exhibits marked heterogeneity in age of onset, tremor type, cognitive involvement, and levodopa responsiveness. Late-onset PD (>70 years) often progresses faster with greater non-motor burden[3]. Atypical tremor morphology (high-frequency, large-amplitude rather than classic 4–6 Hz pill-rolling) and early cognitive dysfunction within 1 year are uncommon in idiopathic PD and can complicate diagnosis and management[4].

Levodopa remains the gold-standard therapy but faces significant pharmacokinetic challenges: delayed gastric emptying (common in elderly patients), competition with large neutral amino acids (LNAAs) from dietary proteins for intestinal and blood–brain barrier transport via the LAT1 transporter, and microbial degradation in the gut (e.g., by Enterococcus faecalis via tyrosine decarboxylase). These factors cause substantial intra- and inter-individual variability in plasma levels and clinical response [5-7].

Simple, low-cost bedside optimizations—such as strict 2-hour meal–drug separation and acidic dissolution of tablets in

lemon juice or ascorbic acid—can enhance bioavailability by accelerating disintegration and reducing competition [8]. Recent evidence confirms that lemon juice supplementation increases plasma levodopa concentrations, while ascorbic acid mitigates carbidopa degradation (e.g., by magnesium oxide in laxatives). Gut microbiota modulation further improves response in some patients [9-10].

Emerging novel drug delivery systems (NDDS) address these limitations by providing continuous dopaminergic stimulation: intranasal routes bypass the blood–brain barrier via olfactory/trigeminal pathways; nanoparticle carriers (lipid-based, PLGA, cationic nanosuspensions) enable targeted brain delivery, sustained release, and improved stability. These technologies are particularly relevant for atypical phenotypes with suboptimal oral levodopa response[11-13].

This case uniquely combines three under-reported aspects in a single report: (1) atypical high-frequency large-amplitude tremor in confirmed idiopathic late-onset PD, (2) early executive cognitive dysfunction suggesting accelerated frontostriatal involvement, and (3) practical pharmacokinetic optimization using lemon juice dissolution plus meal separation—strategies rarely emphasized together in published literature[14-15].

Although levodopa pharmacokinetics has been extensively studied under controlled experimental conditions, there remains a significant gap in translating these principles into routine bedside clinical practice, particularly in elderly patients with atypical presentations. Most available studies focus on pharmacological mechanisms or advanced drug delivery systems, with limited emphasis on simple, cost-effective interventions that can be readily implemented in resource-constrained settings. This case was therefore undertaken to demonstrate the real-world applicability and clinical impact of pharmacokinetic optimization strategies in an atypical late-onset Parkinson's disease patient.

Despite extensive literature on Parkinson's disease, there is limited clinical documentation integrating atypical tremor morphology, early cognitive involvement, and practical pharmacokinetic optimization strategies in a single patient. This case addresses that gap by combining phenotypic variation with real-world bedside therapeutic modulation, thereby providing translational relevance beyond theoretical pharmacokinetic discussions.

Case Report

Patient Information

Case Presentation

A 79-year-old man presented with insidious onset of slowness of movement, difficulty walking, and resting tremors over 6–8 months. Symptoms interfered with daily activities (dressing, writing, walking). There was no history of head trauma, dopamine-blocker exposure, prior neurological disease, or family history of movement disorders.

Clinical Findings

Findings included bradykinesia, reduced arm swing, shuffling gait with reduced stride length, mild upper-limb rigidity, and asymmetrical resting tremor (left > right). The tremor was high-frequency and large-amplitude (distinct from classic pill-rolling), intensifying with emotional stress or mental concentration.

Timeline

Symptoms began 8 months prior to presentation, with gradual progression. Cognitive symptoms appeared within 12 months of motor onset.

Cognitive Assessment

Within 12 months of motor onset, executive dysfunction emerged (impaired planning, attention, decision-making), along with mild memory and attention deficits, indicating early frontostriatal and cortical network involvement.

Diagnostic Assessments

MRI brain, complete blood count, metabolic panel, thyroid function, and vitamin B12 were normal. No structural or metabolic causes of parkinsonism were identified.

Differential Diagnosis

Atypical parkinsonisms were excluded clinically and radiologically (no vertical gaze palsy, severe autonomic failure, apraxia, or alien-limb phenomenon).

Table 1. Diagnostic Comparison: Idiopathic PD vs Atypical Parkinsonisms[16]

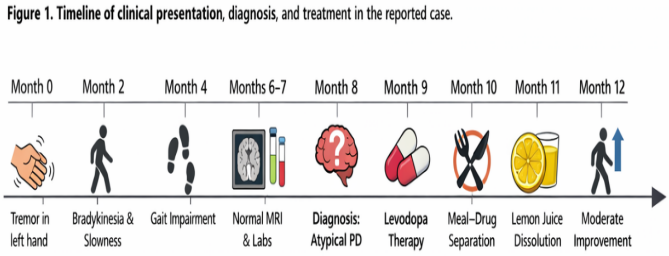
Feature	**Parkinson's Disease (PD)**	**Progressive Supranuclear Palsy (PSP)**	**Multiple System Atrophy (MSA)**	**Corticobasal Degeneration (CBD)**
Age at onset	55–70 years (late possible)	>60 years	55–65 years	60–70 years
Tremor	Classical resting pill-rolling (atypical possible)	Usually absent/mild	Rare (higher frequency, lower amplitude, jerky)	Rare
Rigidity	Common	Severe axial	Present	Asymmetric
Bradykinesia	Core	Present	Present	Present
Postural instability	Late	Early falls	Early	Present
Cognitive impairment	Usually late	Early frontal	Mild–moderate	Prominent cortical
Levodopa response	Good	Poor	Poor/transient	Poor
Relevance to case	Matches (asymmetrical tremor, partial response)	Excluded (no gaze palsy)	Excluded (no severe autonomic failure)	Excluded (no apraxia)

Therapeutic Intervention
Levodopa–carbidopa (Syndopa) was initiated:
110 mg at 6:00 AM, 12:00 PM, 6:00 PM
Controlled-release 250 mg at bedtime

Meal–Drug Separation:
Strict 2-hour interval from protein-rich meals to minimize LNAA competition.

Enhancement of Dissolution:
Tablets dissolved in lemon juice (acidic pH ~2–3) before ingestion to accelerate disintegration and absorption.

Follow-up and Outcomes
Within 4 weeks, moderate reduction in tremor intensity, improved gait speed, and better daily function were noted. Response remained less robust than in classical PD, consistent with phenotypic variation.
This case report has been prepared in accordance with the CARE (CAse REport) guidelines to ensure completeness and transparency in clinical reporting
Figure 1. Timeline of Clinical Presentation, Diagnosis, and Treatment



Discussion
This case illustrates late-onset idiopathic PD with two under-recognized phenotypic variants—atypical high-frequency large-amplitude tremor and early executive cognitive dysfunction—while demonstrating immediate, evidence-based pharmacokinetic optimization.

Phenotypic Heterogeneity in PD
PD is a spectrum rather than a single entity. Tremor-dominant and akinetic-rigid subtypes differ in progression

and cognition. The tremor here (high-frequency, large-amplitude, stress-exacerbated) deviates from classic 4–6 Hz pill-rolling and may reflect distinct basal-ganglia circuitry involvement, as described in reviews of tremor heterogeneity in PD and atypical syndromes. Early cognitive impairment (<1 year) is atypical for idiopathic PD and suggests accelerated non-dopaminergic (cholinergic/frontostriatal) degeneration, aligning with recent mechanistic insights into cognitive heterogeneity in late-onset disease.

Pharmacokinetic Challenges of Levodopa

Levodopa absorption occurs primarily in the proximal small intestine and is highly variable due to delayed gastric emptying (prevalent in elderly patients), LNAA competition at intestinal and blood–brain barrier LAT1 transporters, and gut bacterial decarboxylation (e.g., Enterococcus faecalis tyrosine decarboxylase converting levodopa to dopamine, which does not cross the BBB). These mechanisms explain suboptimal response despite adequate dosing[17-19].

Structured meal–drug separation (2-hour protein-free window) and acidic dissolution in lemon juice directly counteract these barriers. Lemon juice supplementation has been shown to elevate plasma levodopa levels by enhancing tablet disintegration in low-pH environments; ascorbic acid similarly prevents carbidopa degradation (e.g., by magnesium oxide). These low-cost interventions are immediately implementable at the bedside and supported by clinical studies[20-21]. Gut microbiota modulation (reducing E. faecalis) offers additional therapeutic potential.

Emerging Drug Delivery Systems

Conventional oral levodopa produces pulsatile dopaminergic stimulation that contributes to motor fluctuations, dyskinesias, and suboptimal symptom control—limitations particularly pronounced in atypical late-onset phenotypes with early cognitive involvement and variable gastrointestinal absorption[22]. Novel drug delivery systems (NDDS) overcome these by enabling continuous dopaminergic stimulation, protection from peripheral metabolism, and targeted brain delivery, thereby stabilizing plasma levels and improving outcomes in patients with incomplete oral response[23].

Intranasal (Nose-to-Brain) Delivery

Intranasal administration bypasses the blood–brain barrier (BBB) entirely via direct olfactory and trigeminal nerve pathways, enabling rapid axonal transport, perineural migration, and paracellular diffusion through opened tight junctions[24]. Mucoadhesive nanocarriers (chitosan nanoparticles, nanoemulsions, thermosensitive Pluronic PF127 gels) prolong nasal residence time (overcoming mucociliary clearance of ~20 min) and enhance permeation. Specific levodopa formulations include chitosan-loaded nanoparticles, wheat-germ-agglutinin-functionalized PLGA nanoparticles, cationic nanocrystalline suspensions (optimized particle size ~161 nm, positive zeta potential +15 mV), and levodopa nanoemulsions (~104 nm). Preclinical studies in MPTP- and 6-OHDA-lesioned rodent models demonstrate 2- to 17-fold higher striatal dopamine concentrations, sustained motor improvement, and reduced oxidative stress compared with oral levodopa[25]. A clinical feasibility trial using a Precision Olfactory Delivery (POD) device showed increased Cmax and AUC with high patient comfort and preference. These systems are especially advantageous in elderly patients with delayed gastric emptying, offering non-invasive, self-administrable, rapid-onset therapy with minimal systemic exposure[9].

Nanoparticle Carriers

Polymeric nanoparticles, particularly poly(lactic-co-glycolic acid) (PLGA), provide high encapsulation efficiency (>80%), biodegradability into non-toxic lactic/glycolic acids, and tunable sustained release via matrix erosion and diffusion (anomalous transport per Ritger–Peppas model)[26]. Examples include levodopa–carbidopa–entacapone PLGA microparticles (14-fold bioavailability increase, 24-hour release), levodopa–benserazide PLGA nanoparticles (2-week subcutaneous sustained release reducing dyskinesia by up to 46%), and WGA-grafted PLGA for enhanced nasal targeting. Lipid-based systems (solid lipid nanoparticles [SLNs], nanostructured lipid carriers [NLCs], liposomes) excel in lipophilic drug loading, co-encapsulation of antioxidants, and high brain uptake; cationic nanosuspensions further improve mucosal adhesion and olfactory uptake. Hybrid pharmacosomes and lecithin-based vesicles have shown superior locomotor recovery and neuroprotection in Wistar rat models. These carriers protect levodopa from gut decarboxylation (Enterococcus faecalis), reduce peripheral side effects, and enable lower dosing frequency[27-29].

Injectable and Continuous Infusion Systems

Subcutaneous portable-pump infusions (ND0612 levodopa–carbidopa and ABBV-951 foslevodopa/foscarbidopa) deliver 24-hour continuous therapy, significantly reducing "off" time and motor complications in advanced PD. Long-acting biodegradable injectable gels (PLGA/Eudragit formulations) achieve once-weekly levodopa–carbidopa release, replacing multiple daily pills while maintaining stable plasma levels[30,13].

Collectively, these NDDS provide continuous rather than pulsatile stimulation, which is critical for preserving cognitive function and mitigating frontostriatal

involvement in atypical presentations such as the current case. Preclinical and early clinical data confirm superior bioavailability, targeted delivery, and reduced fluctuations compared with optimized oral regimens.

While numerous studies have explored levodopa pharmacokinetics and advanced drug delivery systems, they are largely experimental or technology-driven, with limited direct applicability in routine clinical settings. In contrast, this case highlights the importance of translating pharmacokinetic principles into simple bedside interventions that can be immediately implemented without additional cost or infrastructure. The significance of this case lies not in introducing new pharmacokinetic mechanisms, but in demonstrating how existing knowledge can be effectively applied to improve patient outcomes in a real-world scenario, particularly in elderly patients with atypical features and variable drug response. This bridges the gap between theoretical pharmacology and practical clinical medicine.

Novelty of the Case:

This case report is novel for three key reasons. First, it presents an uncommon tremor phenotype—high-frequency, large-amplitude resting tremor—in a confirmed case of idiopathic late-onset Parkinson's disease, which differs from the classical pill-rolling tremor. Second, the presence of early executive cognitive dysfunction within one year of motor onset suggests accelerated non-dopaminergic involvement, which is atypical in idiopathic Parkinson's disease and raises important diagnostic considerations. Third, the report uniquely demonstrates the clinical utility of simple pharmacokinetic optimization strategies—specifically acidic dissolution using lemon juice and structured meal–drug separation—in improving levodopa response. While these strategies are individually described in literature, their combined real-world application and measurable benefit in such an atypical phenotype are rarely reported.

Clinical Implications

Recognition of atypical features warrants earlier consideration of advanced therapies. Bedside pharmacokinetic optimization (meal separation + lemon juice) is simple, inexpensive, and evidence-supported, improving motor function in this case. NDDS represent the next frontier for stable plasma levels and better quality of life in heterogeneous late-onset PD. Individualized approaches—combining phenotypic assessment with tailored delivery—are essential.

Conclusion

This report underscores clinical heterogeneity in late-onset PD and the practical value of pharmacokinetic optimization. Simple strategies yielded moderate motor gains; emerging NDDS may further benefit atypical presentations. Individualized management remains key to optimal outcomes. This case emphasizes that clinically meaningful improvements can be achieved not only through novel drug delivery systems but also through strategic optimization of existing therapies based on pharmacokinetic principles.

Learning Points

- Parkinson's disease may present with atypical tremor morphology and late onset.
- Early cognitive dysfunction can occur in certain phenotypic variants.
- Optimization of levodopa drug delivery (meal separation + acidic dissolution) significantly influences therapeutic response.
- Novel drug delivery systems (intranasal, nanoparticle) may enhance long-term management.

Declarations Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Ethics Committee in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images/tables.

Availability of data and materials

All data generated or analysed during this study are included in this published article. Additional anonymised details are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Author 1 : Conceptualization, clinical evaluation, drafting.
Author 2: Data collection, literature review.
Author 3: Pharmacological analysis and discussion of drug delivery.
All authors read and approved the final manuscript.

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