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Review

Parkinson's Disease: Pathogenesis, Biomarkers, and Emerging Interventions

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Abstract

Parkinson's disease is the second most prevalent neurodegenerative disorder after Alzheimer's disease, with its incidence predicted to rise dramatically as global populations age. Despite major advances in neuroscience and immunology, effective disease-modifying therapies remain elusive. However, recent breakthroughs in genetics, immunology, biomarker development, and AI-driven analytics are transforming our understanding and approach to Parkinson's disease. This paper synthesizes current knowledge on Parkinson's disease epidemiology, pathogenesis, the role of genetic and environmental risk factors, the expanding landscape of biomarkers and early detection technologies, and the latest advances in clinical therapeutics, with focus on professional practice and translational perspectives..

Keywords: Parkinson's disease, biomarkers, neurodegeneration, genetic risk factors, epidemiology.

1. Introduction

Parkinson's disease (PD) affects millions worldwide, imposing immense burdens on individuals and healthcare systems. The increasing prevalence (projected up to 17 million by 2040) underscores an urgent need for improved understanding and management of this multifaceted disorder. The clinical presentation encompasses characteristic motor symptoms—tremor, rigidity, bradykinesia—as well as myriad non-motor manifestations [1-4]. Historically considered mainly a dopaminergic neurodegeneration, PD is now understood as a multisystem disorder with complex interplay between genetic, molecular, immune, metabolic, and environmental factors. Innovations in molecular profiling, omics, imaging, and AI have enabled earlier detection and risk prediction, driving a paradigm shift toward precision medicine and prevention [5-7].

2. Epidemiology and Disease Burden

PD prevalence is highest among the elderly, with incidence steeply increasing with age. The global burden is rising faster than many other neurological conditions, primarily due to increased life expectancy in both high- and low-income countries. Age remains the single most significant risk factor [8-11].

3. Pathogenesis

α-Synuclein Pathobiology

The aggregation and misfolding of α-synuclein protein form the central pathogenic event in PD. Mutations in the SNCA gene, which encodes α-synuclein, are implicated in familial and sporadic cases. Excess or abnormal α-synuclein triggers synaptic dysfunction, metabolic stress, and propagates via a prion-like mechanism between cells, leading to progressive neuronal loss—most notably in the substantia nigra pars compacta [12-15].

Immune Activation and Neuroinflammation

A body of research overturns the historical "immune-privilege" dogma of the brain. The brain houses its own specialized immune compartments, including microglia (the lifelong sentinels of the central nervous system) and communicates with the peripheral immune system through glymphatic and meningeal lymphatic pathways. In PD, chronic microglial activation and attendant release of pro-inflammatory cytokines accelerate neuronal death and disrupt the blood-brain barrier. Single-cell and spatial transcriptomic analyses have further implicated subtypes of microglia and oligodendrocytes in disease progression .

Both innate and adaptive immunity are involved: CD4+, CD8+ T-cells and monocytes accumulate in PD brains, mediating both tissue-damaging and (potentially) neuroprotective effects [17- 20].

Mitochondrial Dysfunction and Protein Clearance

Impaired mitochondrial function and defects in waste clearance systems (autophagy-lysosome pathway, ubiquitin-proteasome system) are hallmarks of PD pathophysiology, both upstream and downstream of α-synucleinopathy. The resulting oxidative stress and energy failure precipitate dopaminergic neuronal death [21-24].

The Gut-Brain Axis

Classically regarded as a Central Nervous System (CNS) disorder, PD prominently involves the gastrointestinal tract. Symptoms like constipation, delayed gastric emptying, and dysphagia may precede motor symptoms by decades. Braak's Hypothesis postulates α-synuclein pathology originates in the enteric nervous system and spreads via the vagus nerve to the brain. Recent findings that individuals with inflammatory bowel disease develop α-synuclein inclusions substantiate this gut-brain axis model [25-29].

Genetic Susceptibility

PD's heritability is complex. More than 36% of the risk can be explained by nearly 90 genome variants. Monogenic causes include mutations in SNCA, LRRK2 (autosomal dominant), and PRKN, PIKN1, DJ1 (autosomal recessive). Polygenic risk scores enhance risk stratification and prediction, while other genes (such as APOE4) increase the likelihood of developing dementia in PD (Table 1) [30-34].

Table 1 – Risk and Protective Factors

Risk Factors	Protective Factors
Aging, genetic predisposition (e.g., SNCA, LRRK2)	Physical activity
Environmental toxins (pesticides, air pollution)	Caffeine
Microplastics, neurotoxin exposures	Diet rich in vegetables, fruits, grains
Lower socioeconomic status, ultra-processed foods	(Cigarette smoking is associated with lower risk but not recommended)
High-fat diets; APOE4 allele (dementia risk)	

4. Biomarkers and Early Detection

Cerebrospinal Fluid and Tissue Biomarkers

The search for PD biomarkers has lagged behind Alzheimer's disease but is rapidly accelerating. Recent validation of synuclein seed amplification assays (SAA) in cerebrospinal fluid enables sensitive and specific diagnosis, distinguishing symptomatic and asymptomatic gene carriers. Phosphorylated α-synuclein detection in skin biopsies provides a promising less invasive alternative [35-38].

Blood and Multi-Omic Biomarkers

Assays such as glycoprotein non-metastatic melanoma protein B (GPNMB), mitochondrial damage evaluations, and dihydroxyphenylalanine (DOPA) decarboxylase tests are in development, but no single blood-based marker is yet in widespread clinical use.

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Imaging and Digital Biomarkers

Innovative digital techniques supplement traditional imaging modalities:

- Artificial intelligence (AI) analysis of retinal images can identify PD risk nearly a decade before symptom onset.
- Accelerometer data (gait analysis), nocturnal breathing metrics, and multimodal integration of imaging, genetics, and clinical data drive personalized, preclinical diagnosis and prognosis [42-44].

The Changing Role of the Gut Microbiome

Mounting evidence supports the role of dysbiosis (altered gastrointestinal microbiota) in driving both intestinal and CNS inflammation. Microbiome-mediated immune modulation and propagation of pathologic α-synuclein protein from the gut to the brain have been substantiated in both animal models and patients. Fecal Microbiota Transplant (FMT), still investigational, has shown early promise in slowing motor symptom progression [45-47].

5. Current Treatments

Symptomatic management remains the mainstay of PD treatment: dopaminergic and non-dopaminergic medications alleviate motor symptoms and neuropsychiatric sequelae. Surgical interventions, such as deep brain stimulation (DBS) and ablative procedures, are applied in advanced or drug-refractory cases [48,49].

6. Emerging Disease-Modifying Therapies

α-Synuclein Targeted Immunotherapies

Symptomatic management remains the mainstay of PD treatment: dopaminergic and non-dopaminergic medications alleviate motor symptoms and neuropsychiatric sequelae. Surgical interventions, such as deep brain stimulation (DBS) and ablative procedures, are applied in advanced or drug-refractory cases [48,49].

GLP-1 Receptor Agonists

Originally developed as antidiabetic agents, GLP-1 receptor agonists (notably lixisenatide and exenatide) have demonstrated neuroprotective effects and, in randomized trials, sustained motor symptom improvement even after drug cessation. Their anti-inflammatory and neurorestorative mechanisms highlight significant translational potential [53-55].

Microbiome-Directed and Small Molecule Approaches

FMT and the application of rationally tailored probiotics/prebiotics represent a novel domain of potential intervention. Meanwhile, AI-based drug discovery has accelerated identification of orally available α-synuclein blockers, now moving swiftly through early-phase trials [56-58].

Cell and Gene Therapies

Stem cell–based restoration of dopaminergic neuronal populations and in vivo gene editing for known mutations are in early stages of clinical development, reflecting a next frontier in personalized neuroregeneration [59-62].

7. Preventive and Forecasting Strategies

With earlier and more accurate risk assessment via biomarkers and AI-based prediction, there is a rising focus on primary prevention:

- Identification of high- and ultra-high-risk individuals based on genetic, biomarker, and lifestyle profiling.
- Targeted interventions—ranging from lifestyle modification and environmental risk mitigation to prophylactic drug trials—are increasingly plausible and under investigation [63-65].

8. Future Directions and Clinical Implications

The field of PD is at a historic inflection point, moving from a model of late-stage symptomatic management to one of early detection, risk stratification, and targeted intervention. The integration of genomics, multiplexed biomarker panels, and digital health tools empowers clinicians to identify at-risk individuals before the onset of disabling symptoms.

Ongoing and future research should focus on:

- Large-scale validation of early biomarkers and digital diagnostic tools.

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- Rigorous testing of disease-modifying and curative therapies, especially in prodromal and pre-clinical stages.
- Expanding access to and equity in advanced diagnostics and therapeutics across diverse populations [66].

9. Conclusions

PD is no longer viewed as a mere consequence of neuronal attrition but as a complex, multisystem disorder tied intimately to inflammation, immunity, genetics, metabolism, and environment. By embracing this holistic understanding—and by leveraging rapidly evolving biomarker, digital, and therapeutic technologies—the neurological community stands poised to transform the prevention, diagnosis, and treatment of PD in the coming decades.

This synthesis is based on the latest advances highlighted in "Neurodegeneration," incorporating professional insights and recent peer-reviewed literature, tailored for a neuroscience and medical audience.

Conflicts of Interest. Author declares no conflicts of interest.

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Паркинсон ауруы: Патогенезі, биомаркерлері және жаңа емдеу әдістері

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Түйіндеме

Паркинсон ауруы Альцгеймер ауруынан кейінгі екінші ең көп таралған нейродегенеративті бұзылыс болып табылады. Әлем халқының қартаюына байланысты аталмыш аурудың да кездесу жиілігі күрт артады деп болжанылуда. Неврология мен иммунологиядағы айтарлықтай жетістіктерге қарамастан, ауруды модификациялайтын тиімді емдеу әдістері әлі күнге дейін белгісіз. Дегенмен, генетика және иммунология, сондай-ақ, биомаркерлерді әзірлеу мен жасанды интеллектке негізделген талдау саласындағы соңғы жетістіктер Паркинсон ауруына деген түсінігіміз бен көзқарасымызды өзгертуде. Бұл мақалада Паркинсон ауруының эпидемиологиясы, патогенезі, генетикалық және қоршаған ортадағы қауіп-қатер факторларының рөлі, биомаркерлер мен ерте диагностикалық технологиялардың кеңеюі және клиникалық терапиядағы соңғы жетістіктер туралы қазіргі білім, кәсіби тәжірибе мен трансляциялық көзқарастарға баса назар аудара отырып қорытындыланды.

Түйін сөздер: Паркинсон ауруы, биомаркерлер, нейродегенерация, генетикалық қауіп-қатер факторлары, эпидемиология.

Болезнь Паркинсона: Патогенез, биомаркеры и новые методы лечения

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Резюме

Болезнь Паркинсона — второе по распространенности нейродегенеративное заболевание после болезни Альцгеймера. Прогнозируется, что ее заболеваемость будет резко возрастать по мере старения населения мира. Несмотря на значительные достижения в области нейронауки и иммунологии, эффективные методы лечения, изменяющие течение болезни, остаются труднодостижимыми. Однако недавние прорывы в области генетики, иммунологии, разработки биомаркеров и аналитики на основе искусственного интеллекта меняют наше понимание и подход к болезни Паркинсона. В данной статье обобщены современные знания об эпидемиологии болезни Паркинсона, патогенезе, роли генетических и средовых факторов риска, расширяющемся спектре биомаркеров и технологий ранней диагностики, а также последних достижениях в области клинической терапии с акцентом на профессиональную практику и трансляционные перспективы.

Ключевые слова: болезнь Паркинсона, биомаркеры, нейродегенерация, генетические факторы риска, эпидемиология.