

PARKINSON'S DISEASE: UNDERSTANDING OF PATHOBIOLOGY, CLINICAL DIAGNOSIS, BIOMARKERS AND EMERGING THERAPEUTIC STRATEGIES

Neuro Science

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ABSTRACT

Parkinson's disease is a neurodegenerative condition with progressive deterioration of brain functions that leads to motor control problems such as motor deficits, muscle rigidity and tremor; symptoms may present as combinations. Patients with Parkinson's disease often present with non-motor symptoms in addition to the motor ones. The pathobiology of Parkinson's disease is characterised by the degenerative loss of dopaminergic neurons and dysregulation of alpha-synuclein with dysfunctional cellular energy and waste management and neuroinflammatory processes; both genetic and environmental factors are involved. The diagnosis of Parkinson's disease is primarily clinical, with investigative tools that can help in specific circumstances. The gold standard for therapy remains levodopa for the management of motor deficits, with the need for a multidisciplinary care approach for comprehensive management. Emerging strategies are focusing on disease modification. No specific therapy has been consistently demonstrated to be effective for all patients with the condition. This review synthesizes the current understanding of this condition in terms of pathobiology, diagnosis and therapeutic approaches with an emphasis on the evidence and limitations of the available information. Since the review is a narrative and not a systematic review of the literature, it does not make any claims of providing data, numbers or conclusions from the analyses of individual investigations.

KEYWORDS

Parkinson's Disease, Alpha-synuclein, Dopamine, Biomarkers, Seed Amplification Assay, Levodopa, Neurodegeneration, Disease Modification.

INTRODUCTION

Parkinson's disease is one of the most common progressive neurodegenerative conditions that become more prevalent with advancing age, although it can present in younger individuals.^[1] Symptoms of Parkinson's disease are not exclusively motor-dysfunctions associated with sleep, defecation, olfaction, mood disorders, anxiety, pain and autonomic and cognitive functions can develop concurrently with or independently of motor deficits. This heterogeneity reflects the variability of the involvement of different brain regions and the diverse aetiologies of the condition.^[2] A challenge to the diagnosis of Parkinson's disease is the fact that the condition encompassing the label Parkinson's disease may involve a range of diverse populations. The prototypical hallmark of Parkinson's disease involves the loss of pigmented neurons in a region of the brain known as the substantia nigra and the deposition of proteinaceous structures containing alpha-synuclein in multiple brain regions, although this is not consistently detected. Some forms of Parkinson's disease are associated with genetically-determined dysfunctional cellular processes such as waste management and energy metabolism; the environment and aging are also key factors. It proves difficult to predict the development of the condition based on one factor alone.^[2,7] This review aims to provide an overview of the current understanding of the pathobiology of Parkinson's disease, its diagnosis, biomarkers and therapeutic options with an emphasis on the proven aspects and the research gaps.^[1-3,7]

REVIEW APPROACH

This is a review for clinicians and researchers which utilizes the appropriate diagnostic guidelines, treatment recommendations, major reviews and investigations on alpha-synuclein and disease modification. It is not a comprehensive review of the literature as no complete search strategy, systematic methodology, protocol or analytical pooling of information was performed.^[1-9]

SIGNS AND DIAGNOSIS

Movement symptoms

The Movement Disorder Society provides specific signs for the diagnosis of Parkinson's disease and these include the presence of bradyphrenia along with either resting tremor or rigidity. The diagnosis then relies on the identification of supporting signs, red flags and factors for exclusion. Resting tremor is common but not invariably present; postural instability tends to worsen with progression. Upper limb rigidity, dysgraphia and festination of the arms during walking can also be observed.^[1]

Non-movement symptoms

Non-movement symptoms can significantly impact the quality of life of patients with Parkinson's disease and can also present prior to or independently of movement symptoms. These include hyposmia,

constipation, REM sleep behaviour disorder, depression, anxiety, pain, orthostatic hypotension, voiding dysfunction, fatigue and impairments in cognition. These are not exclusive to Parkinson's disease and require careful evaluation.^[2,4]

Diagnosis rules

Parkinson's disease is diagnosed primarily by a qualified clinician based on a detailed history and neurological examination. When diagnostic uncertainty exists, monitoring follows. A clear response to dopaminergic agonists can aid the diagnosis, although this is not sufficient on its own. Investigations including imaging can help exclude other conditions. A dopamine transporter scan can be useful in certain circumstances, but does not definitively differentiate Parkinson's disease from other similar conditions. Genetic screening can be considered based on the age of onset, family history, geographical origin and the potential impact on management or eligibility for a clinical trial.^[1,3,8] Biomarkers are being increasingly utilized, but should not be viewed as readily available tools or a substitute for a thorough clinical examination. The interpretation of such tests depends on the method used, specimen type, populations studied and the purpose of the investigation.^[5,6]

DISEASE PROCESS

Loss of dopamine-producing cells

The degenerative loss of dopamine-producing cells in the substantia nigra reduces the inhibitory inputs modulating movement and explains, at least partly, the efficacy of levodopa, a dopamine precursor, for the management of motor deficits in Parkinson's disease. Parkinson's disease encompasses other brain regions which are partially responsible for the lack of response of certain symptoms to dopaminergic agonists.^[2,3]

Alpha-synuclein and protein management

Alpha-synuclein is a protein that can misfold and aggregate into pathological structures in the brain. These proteinaceous structures have been identified as a neuropathological hallmark of Parkinson's disease. Experimental investigations suggest that there are multiple mechanisms that lead to the pathology and propagation of these structures, although it is not apparent whether one process is consistently more relevant for the development of the condition in a given population. The role of alpha-synuclein is not uniform across different forms of Parkinson's disease and the disease process differs in each individual.^[2,5,6]

Mitochondria, lysosomes and genes

Genetic investigations have demonstrated that multiple genes including SNCA, LRRK2, PRKN, PINK1, PARK7, GBA1 amongst others contribute to the risk for or presentation of specific forms of Parkinson's disease. These genes are associated with the production or

regulation of alpha-synuclein and cellular energy, waste management and response to stress. Most cases are not directly attributable to a clearly identifiable genetic risk factor. Genetic studies are useful in research and clinical practice, but their interpretation can depend on the nature of the genetic variant and individual circumstances.^[2,7]

Inflammation and the environment

The potential contribution of microglia, astrocytes and the neuroendocrine system to the pathogenesis of the condition is being increasingly investigated. Reports suggest that exposure to certain environmental toxins, occupational hazards and head trauma can contribute to the development of the condition, although these factors are challenging to interpret due to the contribution of other variables. A putative environmental risk factor is insufficient in itself to explain the development of an individual case of the condition.^[2,7]

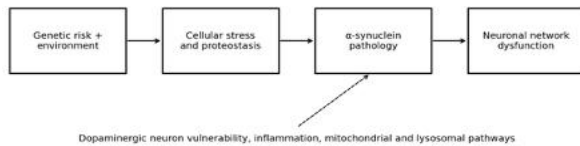


Figure 1 A schematic diagram presenting interrelated processes involved in Parkinson's disease. The diagram represents conceptual associations and not a clear cause-effect mechanism.

BETTER DIAGNOSIS

Alpha-synuclein testing

Testing for alpha-synuclein can indicate whether a given sample has the potential to produce proteinaceous structures under specific conditions. Studies have identified that these tests can be utilised in certain populations with variable sensitivity and specificity that depend on the population and particular challenges to protein formation. Such tests are useful in research to stratify populations and identify eligibility for a clinical trial. Availability, methodological variation and interpretation can vary depending on the population or test used.^[5,6]

Scans and body fluids

Dopamine transporter scans are useful in investigations of the functionality of the dopaminergic system, but are insufficient for the diagnosis of Parkinson's disease. Structural magnetic resonance imaging can be informative for the exclusion of other conditions, but is not helpful in distinguishing Parkinson's disease from other similar conditions. Investigation of blood biomarkers, cerebrospinal fluid, cell-derived particles and other findings are ongoing, but no single investigation has supplanted the need for a clinical evaluation in all situations.^[3,8]

Toward stratification

The combination of the assessment of symptoms, genetic risk, alpha-synuclein tests, imaging and response to management can provide valuable insights for research. The value of a test must be viewed according to the intended purpose-diagnosis, prognosis of the natural history of the condition, investigation into the efficacy of a drug or the ability to predict response to therapy are different considerations that require different types of evidence.^[5,6]

Table 1 Different domains, examples and diagnostic approaches

Domain	Examples	Approach to diagnosis
Movement	Bradyphrenia, rigidity, resting tremor	Assessment of gait changes; note the onset, laterality, progression and response to medication
Sleep/senses	REM sleep behaviour disorder, hyposmia, excessive daytime sleepiness	History and examination; symptoms alone are insufficient
Body functions	Constipation, orthostatic hypotension, voiding dysfunction	Exclusion of other causes; assess orthostatic BP if indicated
Mood/thinking	Depression, anxiety, cognition	Examination of impact; consider other conditions and treatment response

Biomarker/scans	Dopamine transporter scans, alpha-synuclein assays, MRI	Use appropriately; consider validity and availability
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TREATMENT AND CARE

Medication for symptoms

Levodopa combined with a peripherally active dopaminergic agonist is the medication for multiple motor symptoms. The choice and utilisation of medication depend on the symptoms, age, occupation, comorbidities, personal preferences and risk of adverse effects. Dopaminergic agonists and other pharmacological approaches can be effective in some individuals and present with distinct challenges, primarily related to behavioural and sleep disturbances. Always consult a physician before altering medication.^[3,9]

Modifications to symptoms and advanced treatments

The progressive loss of response to medication can occur in some individuals as the condition progresses and alternative strategies such as adjunctive treatments or surgery for deep brain stimulation can be considered. Adjustments to medication regimes or the incorporation of other pharmacological or surgical interventions can be considered for individuals with motor fluctuations. The benefits of these interventions depend on the patterns of symptoms, cognition, comorbidities and specialist assessment.^[3,9]

Therapy and care for non-motor symptoms

Exercise, physiotherapy, occupational therapy, speech therapy and dietary management are key components of care. Effective strategies for falls prevention, sleep management and treatment of mood and body function dysfunctions are included in a multidisciplinary supportive care plan. A team of specialists can address issues that cannot be resolved by medication alone.^[4,8]

Therapies that modify the disease

Research is investigating the role of alpha-synuclein, LRRK2, GBA1-associated pathways, cellular energy, waste management, inflammation and response to stress. A putative mechanism of disease or a specific indicator of a change in disease status is not sufficient for the determination of the efficacy of a treatment. Claims of disease modification require controlled investigations with conclusive evidence and follow up. Currently, no treatment has been proven to be efficacious for all individuals with the condition.^[6,7]

Table 2 Treatment. Evidence considerations

Approach	Primacy	Evidence/limitations
Levodopa-based therapy	Improves bradykinesia, rigidity and other dopamine responsive symptoms	Established symptomatic treatment, does not prove disease modification
Dopamine agonists, MAO B inhibitors	Selective treatment or adjunctive	Individualised consideration of benefits/risk; adverse effects differ between classes
Physiotherapy and exercise	Improves mobility, balance, conditioning	Essential supportive care; appropriate to individual capacity and safety profile
Deep brain stimulation, device assisted therapy	Selective patients with disabling motor fluctuations or tremor	Specialist selection required; does not consistently address non motor symptoms or progression
Alpha synuclein targeted and pathway directed therapies	Investigational disease modification	Requires controlled trials; target engagement is insufficient
Biomarker guided trials	Stratification of participants and target biology assessment	Requires assay standardization and validation for the intended use

RESEARCH PRIORTIES

1. Prospective validation of biomarkers in well-characterised populations.
2. Standardisation of specimen collection assay reporting for alpha

synuclein seed amplification methods.

3. Design trials around defined subgroups while retaining clinically meaningful outcome measures.
4. Improving population recruitment and report age, sex, ancestry, disease stage and comorbidity transparently.
5. Integration of motor non motor functional and patient reported outcome measures in trials.
6. Distinguishing risk association, causal mechanism, target engagement and clinical efficacy in publications.

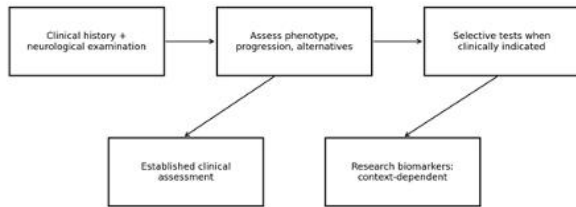


Figure 2 Schematic diagram of considerations in assessment, differential diagnosis, selective testing and research biomarkers contributing complementary information. This is not a decision algorithm for clinical evaluation.

LIMITATIONS

This is a narrative review and not a review. It does not provide search strategy, evidence grading, pooled effect estimates or formal risk of bias assessment. Biomarker performance and regulatory availability can rapidly evolve and differ according to populations and jurisdictions.^[1,9]

CONCLUSION

Parkinsons disease is a neurodegenerative condition with dopaminergic neuronal degeneration and multiple biological interactions. Diagnosis is based on assessment with alpha synuclein seed amplification assays and other biomarkers offering opportunities for biological stratification. Current care includes symptomatic medications and multidisciplinary management. Disease modifying approaches remain a research priority and claims of efficacy should be based on controlled clinical outcomes rather than mechanism. Better biomarker validation, subgrouping, and transparent clinical trials are critical to precision care.

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