Current perspectives on diagnosis and therapy of Parkinson's disease

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In October 2023 the S2k DGN guidelines for Parkinson's disease were disseminated [1]. Subsequent sections detail the alterations and recommendations therein.

Nomenclature

The decision to replace the term Idiopathic Parkinson Syndrome with the broader term Parkinson's Disease (PD) represents a significant step in classifying this condition. It is based on the recognition that a considerable number of Parkinson's cases are not truly idiopathic. Instead, genetic variants, mutations, or environmental factors such as pesticides play a role in the etiology of the disease. Implementing this new nomenclature offers the opportunity to capture the diversity of causes more accurately and provide a more precise description of the condition.

Diagnostics

The updated recommendations for Parkinson's disease diagnosis emphasize a more comprehensive and precise approach. Alongside specific guidelines for genetic testing in humans and a reevaluation of imaging techniques, additional diagnostic procedures are recommended. Special attention is directed towards detecting a prodromal phase, supported by defined criteria, employing cranial magnetic resonance imaging, and conducting polysomnographic examinations in sleep laboratories for early diagnosis. However, it should be noted that genetic testing is presently only conducted in specific conditions and does not yet carry direct therapeutic implications. Genetic testing is recommended only in cases of familial interest or when the disease manifests before the age of 50.

In addition to traditional diagnostic motor features such as bradykinesia, rigidity, and resting tremor, also non-motor signs and symptoms should be considered for establishing the clinical diagnosis. Furthermore, it may be helpful to perform Levodopa tests and to provide long-term treatment with close monitoring of patients, potentially adjusting therapy as needed. Objective testing, such as using Sniffing Sticks alongside patient interviews, is recommended. Imaging techniques such as cerebral magnetic resonance imaging are also recommended. Nuclear medicine diagnostic procedures may be considered but should not be routinely conducted.

Beyond the current guideline recommendations, a new diagnostic method termed SynNeurGe research criteria has been proposed which aims to establish a purely biological approach to Parkinson's disease diagnosis [2}. The primary objective is to develop a biologized concept of PD, facilitating the formulation of disease-modifying therapies. This involves defining a multidimensional framework for subcategorizing the PD spectrum for research purposes and distinguishing the clinical syndrome from its underlying biology. The proposed SynNeurGe system comprises three key components:

1. **Synuclein:** This component focuses on the pathological accumulation of alpha-synuclein in tissue or positive results from alpha-synuclein seeding aggregation tests (SAA). Significant progress has been made in developing SAAs for alpha-synuclein, enabling the identification of "Parkinson-type synucleinopathy" characterized by pathological alpha-synuclein supporting Lewy pathology and excluding multiple system atrophy (MSA). It is imperative to consider synuclein-negative subtypes associated with specific genetic forms of Parkinson's disease.
2. **Neurodegeneration:** This component involves identifying signs of underlying neurodegeneration, currently determined through specific imaging techniques. It is essential to account for neurodegeneration affecting the nigrostriatal dopamine system and other regions, with validated markers indicating central and peripheral nervous system involvement.
3. **Genes:** Documenting defined gene variants causing or strongly predisposing to Parkinson's disease serves as a crucial upstream component.

Once these three criteria are met, the diagnosis of Parkinson's disease can be made on purely biological grounds. Note that these criteria are currently only considered for research purposes.

Challenges associated with the biological concept of Parkinson's disease include its current proposal solely for research purposes and ethical concerns regarding its application in clinical settings for asymptomatic

individuals. Understanding the natural disease progression in individuals across different biological categories is limited and preventing the progression of Parkinson's disease in its early stages is currently unpossible. Revisions incorporating genetic (e. g., polygenic risk scores), environmental, and biomarker advancements (e. g., S, N, and others) are expected to enhance sensitivity and specificity. Subgrouping patients based on additional biomarkers for selected pathways (e. g., mitochondrial, inflammation), and co-pathologies (e. g., ATN, vascular, inflammatory co-pathologies) further presents opportunities for refinement.

Therapy

The therapeutic recommendations emphasize the importance of an individualized approach taking into account various factors. These include the severity of motor symptoms, the patient's age, the efficacy of substances, of side effects, comorbidities, and psychosocial aspects. While Levodopa remains a standard therapy, other medications such as dopamine agonists and MAO-B inhibitors are considered depending on differential diagnostic indicators. In addition, non-oral therapies such as pump therapies and deep brain stimulation are increasingly being considered as options to achieve better symptom control. Special attention is also given to the management of non-motor symptoms such as pain, bladder dysfunction, sleep disorders, and depression.

The management of Parkinson's disease progresses through distinct stages, each requiring tailored therapeutic interventions:

1. **Initiation of Therapy:**
   - For individuals with disease onset under 70 years of age, dopamine agonists are often preferred.
   - Those over 70 years of age or with multiple comorbidities may benefit mostly from Levodopa.
   - Mild symptomatology may be addressed with MAO-B inhibitors.
2. **Intermediate Treatment Phase:**
   - Combination therapy during this phase is warranted to optimize symptom control.
3. **Advanced Treatment Phase:**
   - Invasive therapies are being implemented

These staged approaches provide a framework for clinicians to navigate the complexities of Parkinson's disease management, ultimately aiming at optimizing therapeutic outcomes and enhance patients' quality of life.

New therapeutic approaches for Parkinson's disease focus on innovative methods to address the underlying pathology and enhance patient outcomes. These include antisense oligonucleotides, designed to selectively inhibit the expression of disease-associated gene products, as well as antibody therapies targeting spreading alpha-synuclein. Additionally, efforts are underway to identify anti-aggregatory substances capable of preventing the formation of toxic protein aggregates. These novel approaches offer potentially effective treatment options that may attenuate disease progression and improve quality of life.

Summary

The updated diagnostic guidelines and the advanced therapeutic recommendations mark a milestone in the treatment of this condition. These changes not only offer a more accurate description of the disease and its causes but also provide hope for improved care and quality of life for patients with Parkinson's Disease. Through the continuous development of diagnostic and therapeutic approaches the foundation is laid for the introduction of disease-modifying therapies which could become a reality in the near future.

References:

1. Höglinger G, Trenkwalder C et al. Parkinson-Krankheit, S2k-Leitlinie, 2023, in: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie. Online: www.dgn.org/leitlinien (last accessed March 12th, 2024)
2. Höglinger GU, Adler CH, Berg D, Klein C, Outeiro TF, Poewe W, Postuma R, Stoessl AJ, Lang AE. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. Lancet Neurol. 2024 Feb;23(2): 191–204

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