PARKINSON'S DISEASE: A CLEARER ROAD TO A RELIABLE DIAGNOSTIC TEST?

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Innovation

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with a mean prevalence of 1350/100,000 in the Netherlands [1]. Several symptoms of the disease, like bradykinesia, rigidity, tremor and depression, facilitate a substantial decrease in the quality of life of PD patients [1]. It is important to have a correct diagnosis for the reasons that 1) the progress of therapeutic interventions that may stop or slow the disease can be monitored, 2) intervening at the onset of disease is of importance for symptomatic therapy options, and 3) distinguishing between PD and other diseases is crucial, since there might be differences in prognosis or treatment responses [2, 3]. To date, however, the current methods of diagnosing PD remain unsatisfying [4]. Therefore, this review will first discuss the current state of art in the diagnosis of PD and its limitations and thereafter it will discuss a promising new diagnostic test.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with a mean prevalence of 1,350/100,000 in the Netherlands [1]. Symptoms include motor symptoms like bradykinesia, rigidity and tremor, as well as mental symptoms, like depression or psychosis. These symptoms all substantially impair quality of life of PD patients. Moreover, the financial burden of PD disease rises with the increasing longevity in the population, which leads to a higher incidence of PD cases with age [1]. In short, PD is due to degeneration of dopamine producing neurons in the substantia nigra pars compacta, resulting in an insufficient dopaminergic input in the basal ganglia. Subsequently, there is less stimulation from the thalamus to the premotor cortex, which causes motor symptoms (Figure 1) [5]. The exact cause of PD is unknown, but is expected to be the result of environmental exposures, ageing and genetic susceptibility [6]. Currently, there is no cure available for PD, but there are treatments that aim to treat the symptoms [5, 6]. A correct diagnosis of PD is important for monitoring the progress of therapeutic interventions that may stop or slow the disease, and to intervene at the onset of disease, which might be helpful in terms of providing symptomatic therapy to elevate disease symptoms in patients [2]. However, current diagnosis in the early stages of PD remains relatively suboptimal for the reason that diagnostic accuracy is only 82.7% [4]. This review will first discuss the current state of the art in the diagnosis of PD and its limitations and thereafter it will discuss a promising new diagnostic test.

Current practice

Current diagnosis of PD is mainly clinical [4, 7]. A precise diagnosis of PD is important for prognostic, therapeutic, clinical, pharmacologic and epidemiologic purposes [4]. At present, however, it is a challenge to diagnose PD with certainty, as the clinical presentation of PD is heterogenous and overlaps with various other syndromes. Examples are progressive supranuclear palsy, essential tremor and the parkinsonian variant of multiple system atrophy, commonly referred to as MSA-P [8]. It is of importance to distinguish between these diseases because of the differences in prognosis and responses to treatment [3]. Especially difficult is early diagnosis, since symptoms of possible alternative diagnoses have not yet emerged and response to dopaminergic treatment is less defined [9]. Consequently, misdiagnosis is common and early diagnosis remains difficult and inadequate [4, 7]. Therefore, the United Kingdom Parkinson's Disease Society Brain Bank has determined some criteria, thereby standardising the diagnosis of PD and increasing the diagnostic accuracy even up to 90% [10, 11]. However, it has been suggested that this percentage is the best that can be achieved with clinical assessment [11].

Furthermore, neuroimaging techniques, such as MRI, PET and SPECT, are used to study patterns in the brain. These techniques make it possible to detect premotor disease, monitor disease progression and provide insight in the effects of therapies modifying the disease. Advances in MRI make it possible to separate PD patients from healthy subjects and show a great promise to do the same in PD patients and other akinetic-rigid syndromes [12, 13]. These techniques can be useful measuring the distribution and degree of atrophy in the brain [8] and can provide information about anatomical and functional connectivity changes in PD patients [14]. However, none of these techniques are recommended for routine use in clinical practice [8]. To date, there are no definitive biomarkers for the diagnosis of PD. Reliable biomarkers are needed to discriminate PD from other syndromes [15], since PD is a disease with an ambiguous clinical picture [16].

A promising new diagnostic test

PD is characterised by the accumulation of Lewy bodies, which are composed of misfolded alpha-synucleins [17]. There is increasing evidence that these abnormal formed proteins are harmful to dopaminergic neurons, thereby contributing to neuronal cell death [18-20]. Extensive research has been done over the past years investigating the role of alpha-synuclein in the cerebrospinal fluid (CSF) as a potential biomarker in the diagnosis of PD. Thus far, results were promising but inconclusive [21]. A few years ago, a novel assay has been developed that detects tiny amounts of aggregates of misfolded alpha-synucleins in the CSF [22]. If a high concentration of proteins is added to the CSF, the misfolded alpha-synucleins will misfold the well-folded proteins, which initiates fibril formation [23]. Thereafter, the proteins start emitting light, indicating that there are misfolded alpha-synucleins present in the CSF [23]. Early detection of misfolded proteins in people with an unclear form of PD assures a quite reliable diagnosis. Up until now, the test has a high sensitivity and specificity, but has only been assessed in confirmed clinical cases and not in equivocal cases [16].

Researchers from Nijmegen and Edinburgh have, therefore, recently evaluated the use of this new test in uncertain, but suspected, cases of parkinsonism. For this, they used CSF samples from patients with suspicion of parkinsonism at the time of lumbar puncture. They found a sensitivity of 75%, a specificity of 95 to 98% and positive predictive values of 93%, with the latter two being high, indicating that the vast majority of patients without diagnosis of parkinsonism and a positive test score will have an underlying alpha-synucleinopathy. One restriction of this test is that it cannot differentiate between PD and multiple system atrophy patients. To overcome this, a combination of biomarkers will probably be necessary. However, this is a promising new test with the potential to become a useful diagnostic tool to help discriminate between alpha-synucleinopathies and other parkinsonian syndromes [16].

Conclusion

To summarise, the current diagnosis of PD is mainly based on clinical examination and imaging techniques can provide additional information about structural and anatomical changes in the brain. However, these diagnostic tools are not optimal. Thus, researchers have been searching for biomarkers as a reliable diagnostic tool for PD. Lately, a new test detecting misfolded alpha-synucleins in the CSF has shown great potential. If similar results are observed in other studies, it can be a valuable addition to diagnostics for PD.

Acknowledgements

RAMS would like to thank neurologist Rick Helmich, PhD, Radboud university medical center, Nijmegen, the Netherlands, for providing the author of this article with feedback.

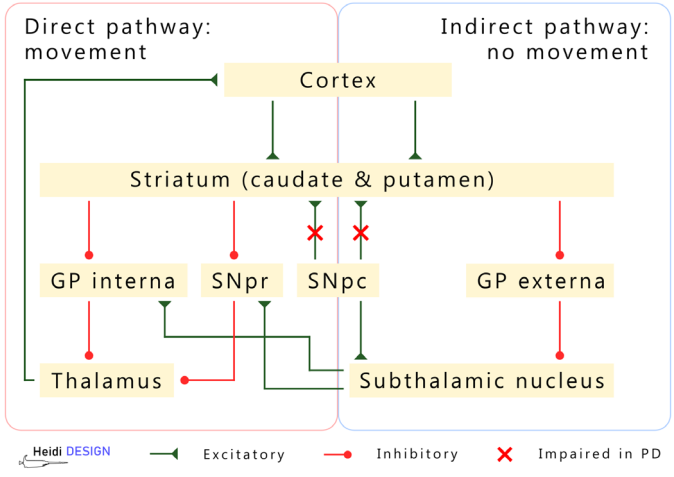

Figure 1: Movement regulating pathways in the basal ganglia in the normal and diseased state

Cells in the Substantia Nigra pars compacta (SNpc) produce dopamine. These cells project on neurons in the striatum (consisting of the caudate and putamen). In the direct pathway (left), excitation of the striatum results in more inhibition of the globus pallidus interna (GP interna) and substantia nigra pars reticularis (SNpr), which in turn leads to less inhibition of the thalamus and thus more activation of movement. In the indirect pathway (right), excitation of the striatum leads to more inhibition of the globus pallidus externa (GP externa), whereafter the subthalamic nucleus is less inhibited and thus more active. This results in more excitation of both the GP interna and SNpr, eventually resulting in inhibition of the thalamus and thereby movement inhibition. In case of PD, the dopaminergic cells in the SNpc degenerate. In both pathways there is less stimulation of the striatum, ultimately resulting in less movement initiation because of over-activity of the indirect pathway and underactivity of the direct pathway.

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