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Recent imaging advances in the diagnosis and management of Parkinson's disease

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Abstract

In this review we report novel sensitive imaging biomarkers for Parkinson's disease (PD) and its atypical variants. Diffusion tensor imaging and transcranial brain sonography are potentially promising techniques that can differentiate typical PD from atypical variants (multiple system atrophy and progressive supranuclear palsy) and from benign tremor disorders. Non-motor symptoms, such as dementia, depression, and sleep disruption, are often more distressing to PD patients than their slowness and stiffness. Dopamine replacement treatment can also lead to complications such as dyskinesias, impulse control disorders, and psychosis. Recent positron emission tomography studies have helped to clarify the physiopathological mechanisms underlying dementia and compulsive gambling in PD and provide a rationale for therapeutic strategies.

Introduction and context

Parkinson's disease (PD), the second most common neurodegenerative disorder, is associated with the presence of intra-neuronal fibrillar aggregates of α-synuclein called Lewy bodies and the degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta. Clinically, patients show a combination of motor symptoms (rest tremor, bradykinesia, rigidity) and non-motor features (dementia, sleep disorders, fatigue, depression) caused by dopamine depletion and, to a lesser extent, dysfunction of other neurotransmitters. The role of non-dopaminergic dysfunction in PD, however, remains unclear, and a better understanding of this area is currently one of the main key targets for PD research.

The diagnosis of PD is still based on clinical symptoms and signs. However, particularly at the onset of symptoms, it may be difficult to discriminate between PD, essential and dystonic tremors, and atypical parkinsonian variants with alternative pathologies, such as multiple system atrophy and progressive supranuclear palsy.

A minority of patients with PD develop compulsive behaviours such as pathological gambling, compulsive shopping, and hypersexuality while receiving dopamine replacement treatment. The anatomical and neurochemical substrates of these behavioural disturbances in PD remain to be established.

Structural and functional neuroimaging techniques provide powerful tools to investigate *in vivo* the physiopathological mechanisms underlying PD. Magnetic resonance imaging (MRI) and, more recently, transcranial sonography (TCS) have been used to detect alterations in nigral structure. New MRI techniques, including diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT), enable evaluation of the integrity of neuronal connectivity in the brain. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are radiotracer-based techniques and can be employed in PD to evaluate: (a) presynaptic dopaminergic terminal function; (b) postsynaptic dopamine receptor function; (c) dopamine

release and changes in extracellular dopamine levels; and (d) dysfunction of non-dopaminergic pathways.

Recent advances

A correct diagnosis of PD is vital in order to establish the correct prognosis of the disease, to predict its response to therapy and last, but not least, to ensure appropriate recruitment of patients into clinical trials testing the efficacy of new putative neuroprotective and symptomatic therapeutic agents. PD is associated with striatal dopamine deficiency and so assessment of presynaptic striatal dopamine terminal function with either PET or SPECT can support or refute the diagnosis. A recent paper reports the results of a direct comparison of ^{123}I-FP-CIT SPECT, a marker of dopamine transporter binding, and ^{18}F-dopa PET, a marker of dopamine storage capacity, in 28 patients with clinically probable PD [1]. These imaging modalities were both able to reliably discriminate early PD patients from healthy controls. Detection of reduced dopaminergic function in the putamen contralateral to the more symptomatic side showed 100% specificity and sensitivity for PD. Longitudinal follow-up studies are required to compare the sensitivity of the two techniques for monitoring progression of nigrostriatal degeneration in PD.

A single 15 minute scan 75 minutes after injection of ^{18}F-dopa seems to be sufficient to discriminate PD patients from healthy controls [2]. The researchers at the Turku PET Centre, Finland analyzed PET images of ^{18}F-dopa uptake with both a traditional method (Patlak graphical analysis of data collected 15-90 minutes after injection) and a region-to-reference ratio (striatal-to-occipital ratio, or SOR) calculated 75-90 minutes after injection. Both methods were able to separate 84 unmedicated PD patients from 21 healthy volunteers. In principle, by shortening the scanning time, a 75-90 minute SOR analysis may offer several advantages, including less discomfort for the patient and reduced subject movement during the scan. It remains to be established whether the snapshot method is sensitive to longitudinal changes in ^{18}F-dopa uptake and whether it can be used in the long-term evaluation of disease progression.

A recent prospective blinded study has assessed the specificity and sensitivity of TCS for the differential diagnosis of PD [3]. TCS measures brain tissue echogenicity through the intact skull and has been used for more than 10 years to discriminate PD from other movement disorders [4-6]. In PD patients, the typical TCS finding is increased echogenicity from the lateral midbrain, probably reflecting increased iron deposition in the SN [3].

In a prospective study, 60 patients with soft signs of parkinsonism had baseline TCS and then were clinically assessed every 3 months for 1 year. At the end of the follow-up period a clinical and/or SPECT/PET diagnosis was made in 53 patients. Thirty-nine were classified as having PD, ten as having atypical parkinsonian syndrome, and four had neither of these two conditions. Compared to the final diagnosis, the sensitivity of TCS at baseline was 90.7% and the specificity was 82.4%. The positive predictive value of TCS for PD was 92.9% with a classification accuracy of 88.3%.

This is a promising result, although there are difficulties with the diagnostic use of TCS. First, increased SN echogenicity has also been reported in 17% of patients with essential tremor [7], 40% of depressed patients without signs of PD [8], and in 10% of age-matched healthy volunteers [9], suggesting the specificity of TCS is suboptimal. Second, while most subjects have a suitable preauricular acoustic bone window, this is not always the case. Finally, patients with severe tremor have to be excluded because movement artefact prevents reliable interpretation of the images. If the presence of tremor interferes with the examination, it could represent a limitation of this method in clinical practice as most PD patients have this symptom.

Assessment of regional fractional anisotropy (FA) within nigrostriatal structures with DTI provides another non-invasive biomarker that can be used to detect PD. FA is a measure of the directional diffusivity of water in tissues and provides information on the integrity of tracts in the cerebral white matter and grey matter. In a recent study, FA in the SN was measured in 14 untreated early stage PD patients and 14 healthy volunteers matched for age and gender [10]. FA values in the SN were reduced in all the PD patients compared to the control group. The greatest difference between the two groups was observed in the caudal part of the SN. The findings are in agreement with post-mortem studies, which show greater cell loss in the ventro-caudal SN compared with the rostral segment of this structure.

The DTI approach enabled accurate discrimination of individual subjects; PD patients were distinguished from the healthy volunteers on the basis of their FA value in the caudal part of the SN with 100% sensitivity and specificity. If confirmed in larger cohorts of PD patients, these findings suggest that DTI could be as sensitive as PET and SPECT for supporting a diagnosis of PD.

Cognitive impairment is one of the most disabling non-motor complications of PD. The incidence of dementia

Table 1. Recent imaging findings in Parkinson's disease

Study	Topic	Imaging technique	Main findings
Eshuis *et al*., 2009 [1]	Disease diagnosis	^{123}FP-CIT SPECT and ^{18}F-dopa PET	Both techniques were equally able to distinguish PD patients from healthy controls (100% specificity and sensitivity)
Jokinen *et al*., 2009 [2]	Disease diagnosis	^{18}F-dopa PET	Striatal-to-occipital ratio calculated from 75-90 minutes after tracer injection (short scan) can be used to separate PD patients from healthy volunteers
Gaenslen *et al*., 2008 [3]	Disease diagnosis	TCS	The positive predictive value of TCS for PD was 92.9% with a classification accuracy of 88.3%
Vaillancourt *et al*., 2009 [10]	Disease diagnosis	DTI	Fractional anisotropy in the substantia nigra was reduced in the PD patients compared to the control group
Lee *et al*., 2008 [18]	Dementia in PD	^{18}F-FDG PET	Cholinesterase inhibitor therapy improved memory in PD patients with dementia and induced significant increases in cerebral metabolism
Steeves *et al*., 2009 [20]	Pathological gambling	^{11}C-raclopride PET	Evidence of increased ventral striatal dopamine release in PD patients with pathological gambling

DTI, diffusion tensor imaging; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single photon emission computed tomography; TCS, transcranial brain sonography.

in PD is about six times higher than that in age-matched healthy people and increases exponentially with age [11]. Two recent papers have reported that amyloid pathology, as measured by ^{11}C-PIB PET, is infrequent in PD patients with later onset dementia [12,13]. These findings would suggest that that ß-amyloid deposition, a pathological hallmark of Alzheimer's disease, does not contribute significantly to the pathogenesis of later dementia in PD. However, this remains to be confirmed in larger PD populations and disease subgroups. In contrast, there is growing evidence that dopaminergic and cholinergic dysfunction may play a role in causing the cognitive deficits observed in PD patients [14-17]. Cholinergic dysfunction can be detected even in early PD [17]. The effect of cholinesterase inhibitor (ChEI) therapy on cerebral glucose metabolism has recently been assessed in 12 PD patients with dementia [18]. ChEI treatment improved memory and induced significant increases in cerebral metabolism in the left angular gyrus (extending to the supramarginal area and left superior and middle gyri), in the right superior, and left middle orbitofrontal gyri. There were significant correlations between improvements in Mini Mental State Examination and increased cerebral metabolism in the left supramarginal, orbitofrontal, and cingulate areas.

Recently, impulse control disorders and other behavioural disturbances, which are generally associated with exposure to dopaminergic medication – particularly agonists, have surged to clinical importance as they can devastate the quality of life for both PD patients and their families. Affected cases have gambled away their life savings on occasion. The mechanisms underlying the development of these behavioural disturbances in PD are currently under extensive investigation.

A recent SPECT study has reported that PD patients with pathological gambling show overactivity in several areas of the reward-related mesocorticolimbic circuitry during resting condition [19]. Moreover, patients with pathological gambling also exhibit greater dopamine release during gambling than control patients as demonstrated by greater decreases in ventral striatum ^{11}C-raclopride binding in the former group of patients [20]. These findings provide evidence that inappropriate brain dopaminergic activity underlies the neurobiology of impulse control disorders in PD. See Table 1 for an overview of recent imaging findings in PD.

Implications for clinical practice

Both PET and SPECT have high sensitivity and specificity for detecting striatal dopamine deficiency and can be useful in supporting or refuting a diagnosis of PD, even in early stages of disease. FP-CIT SPECT is now in widespread use in Europe for this purpose and recently became licensed for use in the US. PET is a more versatile modality than SPECT but more expensive and less available. It will maintain a crucial role in the understanding of the physiopathological mechanisms underlying PD and its complications, but it seems unlikely, at this stage, that it will ever become a routine examination for PD.

SN hyperechogenicity and measures of caudal FA with DTI may prove to be as sensitive as PET and SPECT for the early diagnosis of PD. Both techniques are non-invasive, inexpensive and easy to implement. Nevertheless, these are preliminary findings and need to be confirmed in larger cohorts of patients.

Cholinergic dysfunction plays an important role in causing cognitive impairment in PD. Findings from recent imaging studies provide a strong rationale for the use of ChEI therapy in PD patients with cognitive impairment, possibly even before the occurrence of established dementia.

Abbreviations

ChEI, cholinesterase inhibitor; ^{11}C-PIB, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; ^{18}F-dopa; 6-L-^{18}F-fluorodihydroxyphenylalanine; ^{123}I-FP-CIT, ^{123}I-labelled N-(3-fluoropropyl)-2ß-carbomethoxy-3ß-(4-iodophenyl)nortropane; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; SN, substantia nigra; SOR, striatal-to-occipital ratio; SPECT, single photon emission computed tomography; TCS, transcranial brain sonography.

Competing interests

DJB is Head of Neurology in Medical Diagnostics at GE Healthcare.

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