The Role of Neuroimaging in the Diagnosis of Parkinson’s Disease

Review Article

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Abstract Parkinson’s disease (PD), the second most common neurodegenerative disease, is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the formation of intracytoplasmic Lewy inclusion bodies. To date, the diagnosis of idiopathic PD is mainly based on its cardinal clinical features: resting tremor, bradykinesia and rigidity. In recent years, advances in magnetic resonance imaging (MRI), transcranial sonography (TCS) and functional imaging - which includes positron emission tomography (PET) and single photon emission computed tomography (SPECT) - have provided new tools for the diagnosis of PD in its early stages and have discriminated it from other atypical Parkinsonian syndromes. This review focuses mainly on the current development of neuroimaging and its application in the diagnosis and differential diagnosis of PD.

Keywords Diagnosis, Functional Imaging, Magnetic Resonance Imaging, Transcranial Sonography, Parkinson’s Disease

1. Introduction

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disorder which is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the formation of intracytoplasmic Lewy inclusion bodies [1]. The definitive diagnosis of idiopathic PD needs the histological demonstration of intraneuronal Lewy body inclusions in the substantia nigra pars compacta but this is impractical during life [2]. In early PD, moreover, the full picture of its clinical manifestations (resting tremor, bradykinesia and rigidity) may not yet be overt. PD can be imitated by many other syndromes, such as essential and dystonic tremors, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and vascular Parkinsonism.

To date, up to 20% of the cases thought to be idiopathic PD turn out to be other diseases, despite strict diagnostic criteria being used [3]. In considering this situation, the precise grasping of the altered nigral structure or striatal dopamine terminal function can help to increase diagnostic accuracy for idiopathic PD and rationalize the use of dopaminergic replacement strategies.

Conversely, it is also difficult to discriminate atypical Parkinsonian syndromes from idiopathic PD in their initial stages. Only when the full picture of the syndromes become evident does the diagnostic accuracy of atypical Parkinsonian syndromes improve. These
conditions tend to have a dissatisfied prognosis as well as poor response to levodopa. Novel imaging techniques provide useful tools for detecting striatal pathology, which helps to differentiate them from true idiopathic PD.

2. Imaging midbrain structural changes

2.1 Magnetic resonance imaging

Structural magnetic resonance imaging (MRI) is comprised of MRI-based volumetry, diffusion-weighted (DWI) and diffuse tensor (DTI) imaging. Basic MRI shows a normal nigral structure in idiopathic PD and so is not diagnostically helpful. It is also difficult in applying Volumetric T1-weighted MRI to detect a reduction in nigral volume in PD because of its poor accuracy in identifying the border of the nigra compacta [4]. Diffusion weighted imaging (DWI) or diffusion tensor imaging (DTI) is a MRI-based technique providing quantified diffusion information on the random movement of the water molecules which flow along the fibres tracts in the central nervous system [5]. This diffusion information can be described as isotropy or anisotropy. The latter represents a situation that the diffusion depends upon directions and is quantified as an apparent diffusion coefficient (ADC) by applying the field gradients of different degrees of diffusion sensitization [6]. Neurodegenerative disorders get rid of restraints in water molecule movement, resulting in reducing anisotropy while increasing the ADCs and so proving the disruption of neural tracts. This theoretical analysis provides for the potential utility of DWI and DTI in the diagnosis of idiopathic PD by detecting altered anisotropy and ADCs in basal ganglia. In Vaillancourt’s study, fractional anisotropy and the apparent diffusion coefficient in the substantia nigra was measured in 14 early-stage PD patients and 14 age-matched healthy volunteers [7]. Lower fractional anisotropy values were found in all PD patients in the region of interest, compared with the control group. The reduction in caudal SN, moreover, is greater than that in the rostral region of interest, which is in agreement with post-mortem studies. A sensitivity and specificity of 100% was acquired in distinguished PD patients with the healthy controls on the basis of their fractional anisotropy value in the caudal nigra. In addition, the value of DTI approaches in differentiating between idiopathic Parkinson’s disease and atypical parkinsonism have been discussed in several studies. Boelmans et al. showed that DTI parameters in the corpus callosum can be used to differentiate corticobasal degeneration from idiopathic PD [8]. Nicoletti et al. showed that the apparent diffusion coefficient values of the superior cerebellar peduncle could be used to discriminate patients with PSP from idiopathic PD as well as the Parkinsonian variant of multiple system atrophy (MSA-P) [9]. In the future, newer techniques based on MRI might be increasingly integrated into the diagnosis of idiopathic PD in the future.

2.2 Transcranial Sonography

Transcranial sonography (TCS) displays brain structures by applying an ultrasound probe at the temporal bone window to detect an ultrasound echo. About 90% of cases with clinically defined PD exhibit increased echogenicity - namely hyperechogenicity - at the site of the substantia nigra [10, 11]. In addition, Walter et al. showed that transcranial sonography detected normal substantia nigra echogenicity in atypical PD in contrast with hyperechogenicity in the midbrain of the idiopathic PD patient, suggesting that transcranial sonography could be used as a helpful instrument for the differential diagnosis of idiopathic PD. Moreover, the hyperechogenicity of the lentiform nucleus is present in most atypical PD but absent in idiopathic PD [12]. Normal midbrain signal in combination with lentiform nucleus hyperechogenicity can differentiate atypical from idiopathic PD with a sensitivity of 59% and a specificity of 100%. The midbrain hyperechogenicity, however, remains static over five years despite the progression of symptoms and does not correlate with disease severity in PD [13]. As such, Brooks et al. suggested that the presence of midbrain hyperechogenicity may represent a trait rather than a state marker for susceptibility to PD [14].

3. Functional imaging--positron emission tomography (PET) / Single photon emission computed tomography (SPECT)

3.1 Pre-synaptic dopamine terminal function

Pre-synaptic dopaminergic function can usually be evaluated by three different approaches [15]: (1) the availability of pre-synaptic dopamine transporters (DAT) in charge of the high-affinity uptake of dopamine from the synaptic cleft with 99mTc-TRODAT SPECT or 123I-FP-CIT SPECT; (2) the aromatic amino acid decarboxylase (AADC) activity of dopaminergic neurons with 18F-dopa PET; (3) the density of vesicular monoamine transporter type 2 (VMAT2) located in the vesicular membrane, which is responsible for transporting dopamine from the cytoplasm into secretory vesicles, with 18F-dihydrorymethazine (18F-DTBZ) PET.

Striatal DAT binding reduction in PD is characterized by affecting the posterior more than the anterior in an asymmetric pattern, which has been found in over 90% of clinically probable PD cases [16]. This binding, however, is normal in essential tremor patients or vascular parkinsonism. A multicenter study of dopamine transport imaging compared clinical diagnostic parkinsonism with essential tremor patients by applying 123I-FP-CIT SPECT. Their results showed a high
sensitivity and specificity in differentiating Parkinsonism with non-Parkinsonism (a sensitivity of 98% and a specificity of 83%) [17]. In another study, 99mTc-TRODAT SPECT could distinguish PD from vascular parkinsonism. This evidence, therefore, indicates that DAT imaging could be a valuable means of supporting or rejecting a diagnosis of parkinsonism associated with striatal dopamine deficiency. Several studies have examined the role of DAT imaging for determining whether uncertain Parkinsonian cases are associated with striatal dopamine deficiency. In a small prospective study of 15 subjects with clinically unclear Parkinsonian syndromes, 13 with probable Parkinson’s disease, and 13 healthy volunteers evaluated by using 99mTc-TRODAT SPECT, there was 80% agreement in comparing the baseline SPECT diagnosis with the gold standard clinical diagnosis of PD at 2 years' follow-up, and 100% sensitivity [18], implying its potential use in the diagnosis of patients with clinically uncertain Parkinsonian syndromes.

Detecting pre-synaptic dopaminergic terminal integrity with either striatal 18f-dopa uptake or a DAT SPECT marker, however, exhibits poor effectiveness in discriminating atypical Parkinsonian syndromes from typical PD [19, 20]. The typical gradient of loss of dopaminergic function in PD, however, is also found in some cases of multiple system atrophy [21 22, 23].

3.2 Post-synaptic dopamine receptor binding

Post-synaptic dopaminergic function is mainly assessed by the density of dopamine receptors, which are located in the membrane of the post-synaptic dopaminergic neurons. Generally, dopamine receptors are divided into two families, the D1 family (D1, D5) and the D2 family (D2, D3, D4). The dopamine D1 receptor can be detected by 11C-SCH23390 PET or 123I-BZM SPECT. However, this type of imaging approach is not widely used for there is no evidence of alterations in typical PD [24]. ¹¹C-raclopride (¹¹C-RACLO) PET is employed in order to estimate alterations in the D2 receptor. Several studies showed that the striatal D2 dopamine receptors’ reduction in putamen is more severe in MSA patients than that in PD cases [25, 26], suggesting that the assessment of the striatal dopamine receptor may help differentiate PD from Parkinson plus conditions for clinical practice.

3.3 Glucose metabolism and cerebral blood flow

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET can be used to measure resting regional cerebral metabolic rates for glucose and has become a increasingly popular field for the study of neurodegenerative diseases. By applying a method termed the ‘scaled sub-profile model’ (SSM) - which is a spatial covariance method based on principal component analysis (PCA) - to assess subject-by-region effects in functional brain images [27], Eidelberg et al. have described characteristic patterns of glucose metabolism in different neurodegenerative disorders [28, 29]. The feature of glucose metabolism in PD, which is called a PD-related pattern, is increased metabolism in the basal ganglion and motor cortex as well as a cerebellum with abnormal reductions in parietal- and occipital-associated regions and in the dorsolateral prefrontal cortex. What is more, there are also MSA-related patterns, PSP-related patterns and corticobasal degeneration-related patterns. These patterns, therefore, make it possible for the differential diagnosis of idiopathic PD by employing ¹⁸F-FDG PET. Eidelberg et al. showed that a high sensitivity and specificity was obtained not only in identifying idiopathic PD patients with healthy controls (a sensitivity of 100% and a specificity of 86%), but also in discriminating atypical parkinsonism from idiopathic PD patients (a sensitivity of 96% and a specificity of 91%) by using ¹⁸F-FDG PET and the spatial covariance method [30]. This promising method needs further studies on larger patient cohorts to prove its effectiveness.

3.4 Cardiac sympathetic denervation

¹²³I-metaiodobenzylguanidine (¹²³I-MIBG), which is an analogue of guanethidine and taken up by the post-ganglion sympathetic neurons, is employed to measure the sympathetic nerve system [31]. A number of studies have shown decreased myocardial uptake in early PD patients compared with that in healthy controls. Significantly lower uptake was, moreover, found in idiopathic PD cases than that in atypical parkinsonism, even in very early stages [32,33]. Thus, ¹²³I-MIBG myocardial scintigraphy may offer helpful information in the differential diagnosis of PD in its initial phase, particularly without clinical signs of autonomic failure. Nagayama et al., however, indicated that the high sensitivity but poor specificity of MIBG myocardial scintigraphy in detecting PD (a sensitivity of 87.7% and a specificity of 37.4%, respectively) [34]. More than half of the patients without PD (66.5%) exhibited low MIBG uptake, which contributed to considerable overlap of the ratios between PD and other disorders. Conversely, in another research up to half of the patients with Hoehn and Yahr stage 1 can still show the normal tracer binding [35]. Much more attention should be paid in using myocardial scintigraphy for the diagnosis of idiopathic PD.

4. Conclusion

Developments in neuroimaging have indeed improved the accuracy of the diagnosis of idiopathic PD. Each approach, however, has its own pitfalls that limit its utility in the diagnosis of idiopathic PD. Understanding the limitations will help to make proper use of these techniques.
5. References


