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Neuroimaging in Parkinson's Disease.

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Abstract : Parkinson's disease (PD) is one of the most common neurodegenerative disorder. It is a part of parkinsonian syndrome, and its clinical diagnosis depends on the presence of four cardinal features: bradykinesia, rest tremor, rigidity, or postural instability. In the initial stages, clinical diagnosis of PD and its differentiation from other parkinsonian syndrome is not always a easy task, and many a times as disease advances the earlier established diagnosis may be proved wrong. There are various imaging techniques, specially functional imaging which may be helpful to reach the accurate diagnosis of these parkinsonian syndrome at the earlier stage of disease and therefore to make the physician in better position to institute treatment appropriately as well as to prognosticate more precisely. In this article role of these imaging in various parkinsonian syndromes is discussed briefly. **Key words:** Parkinson's disease, MRI, Functional imaging

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders with an incidence rate of 17 out of 100,000^{1,2}. PD is part of a group of diseases with common features labeled as Parkinsonian Syndrome (PS), including Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA). The true definitive diagnosis of Parkinson disease (PD) requires histologic demonstration of intraneuronal Lewy body inclusions in the substantia nigra compacta, and such demonstration is clearly impractical during life and can only be made from a post-mortem examination of the brain. The nigrostriatal projection loss that characterizes PD is associated with striatal dopamine deficiency

targeting the posterior putamen. The diagnosis of PS until recently was a clinical one, and often proven incorrect with further clinical follow up. Pathology only confirms about 80% of clinically diagnosed PD cases^{3,4}.

In up to 15% of cases labeled as early PD by investigators, imaging has shown normal dopamine terminal function suggestive of an alternative diagnosis^{5,6}. Given this statistics, the ability to noninvasively detect altered nigral structure or striatal dopamine terminal function potentially provides valuable tools that can help increase diagnostic specificity for dopamine-decient parkinsonian syndromes and rationalize management decisions at initial stages of disease.

MRI

Conventional MR imaging is extremely useful for excluding structural abnormalities such as mass lesions, infarcts, or

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hydrocephalus, which may produce symptoms mimicking neurodegenerative disease. Morphologic changes, such as selective lobar atrophy, are typically better visualized on T1-weighted or fluid-attenuated inversion recovery (FLAIR) images, which highlight the contrast of high-signal central nervous system structures against low-signal cerebrospinal fluid⁷. Increased T2 signal typically reflects varying degrees of wallerian degeneration, demyelination, and gliosis, whereas low T2 signal indicates the physiologic accumulation of paramagnetic substances such as ferritin. Similarly DTI Diffusion-Tensor Imaging (DTI), particularly mean diffusivity and fractional anisotropy; has shown promising results differentiating controls, patients with Parkinson disease, from normal subjects and patients with progressive supranuclear palsy⁸. However, these results have been obtained through measurements on structures of the basal ganglia and their connections and do not necessarily reflect the degree of degeneration of the substantia nigra itself. In a recent study, twenty-eight subjects (14 with early stage, untreated PD and 14 age- and gender-matched controls) were studied with a high-resolution DTI protocol at 3 Tesla using an eight-channel phase array coil and parallel imaging to study specific segments of degeneration in the SN (mainly rostral, middle, and caudal SN). A receiver operator characteristic analysis in the caudal SN revealed that sensitivity and specificity were 100% for distinguishing patients with PD from healthy subjects⁹. These findings provide evidence that high resolution diffusion tensor imaging in the substantia nigra distinguishes early stage, de novo patients with Parkinson disease (PD) from healthy individuals on a patient by patient basis and has the potential to serve as a noninvasive early biomarker for PD.

Another promising and useful MR imaging modality, known as inversion recovery is based on changes in the spin-lattice relaxation time (T1), which, seem to accompany nigral degeneration because of degenerative changes in the intracellular compartment and in iron deposition. Inversion-recovery sequences are a convenient and widely available way to obtain images whose contrast heavily depends on the spin-lattice relaxation time (T1) of tissues¹⁰. Compared with advanced MR imaging techniques such as diffusion-tensor imaging and fiber tracking, inversion-recovery imaging may be easier to implement in a clinical routine because acquisition time is limited and post processing of data is very simple.

TRANSCRANIAL ULTRASONOGRAPHY

Transcranial B-mode sonography (TCS) of deep brain structures has been established as a tool for the diagnosis and monitoring of degenerative brain disorders in the past decade. Technological advances have enabled standard applications (assessment of the substantia nigra [SN], measurement of ventricle widths) with sufficient quality even with a portable US-S¹¹. With contemporary high-end US-S, excellent image resolution of deep brain structures is achieved which can be superior to that of magnetic resonance imaging (MRI) under clinical conditions. Compared to MRI and computed tomography, the advances of TCS are its high mobility, short investigation times, non-invasiveness, and low cost. Involuntary head motion in movement disorder patients can be well compensated by the investigator. Most of all, TCS detects abnormalities that are not seen, or only seen with significant effort, with other neuroimaging modalities.

In an initial series, 92% of patients with clinically established PD were reported to show bilaterally increased echogenicity from the lateral midbrain. The size of the transcranial sonography signal,

however, does not correlate well with the disability rating in PD and despite progression of symptoms, remains predominantly static over a follow up period of 5 years¹².

In a recent study, it has been suggested that the presence of midbrain hyperechogenicity is a trait rather than a state marker for susceptibility to parkinsonism and may reflect nothing more than midbrain iron deposition¹³. A prospective study was done to assess the specificity and sensitivity of transcranial sonography for the differential diagnosis of PD in which sixty patients with soft signs of parkinsonism underwent baseline transcranial sonography and then were clinically assessed every 3 months for a period of 1 year. At the end of the follow-up period, 39 were classified as having PD, 10 as having atypical parkinsonian syndromes (which do not show midbrain hyperechogenicity), and 4 as having neither of these conditions. Compared with the final clinical diagnosis, the sensitivity of transcranial sonography for detecting PD at baseline was 91% and the specificity was 82%. The positive predictive value of transcranial sonography for PD was 93%, with an accuracy of 88%¹⁴.

Functional imaging in PD: The function of dopamine terminals in PD can be examined by many ways in vivo which include evaluation of the first step in dopaminergic transmission, namely dopamine synthesis, which takes place in the presynaptic dopaminergic neurons, assessment of the availability of presynaptic dopamine transporters (DAT) with a variety of PET and SPECT tracers, examining the vesicle monoamine transporter availability in dopamine terminals with either 11C- or 18F-dihydrotetrabenazine PET, and by measuring the binding capacity of the postsynaptic striatal D2 receptors by several PET tracers.

EVALUATION OF DOPAMINE SYNTHESIS

The PET tracer 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine ([18F]DOPA) (most commonly used in PD studies) is taken up into neurons by an active transport system and is converted to [18F]dopamine by aromatic amino-acid decarboxylase (AADC), which represents the rate-limiting step in dopamine synthesis in dopaminergic neurons. As such, [18F] DOPA uptake reflects the synthetic ability of dopaminergic neurons to produce dopamine through AADC. Several studies demonstrated a significant reduction of [18F]DOPA striatal uptake in PD patients compared to control subjects. The reduction is more severe in the putamen than in the caudate nucleus, and most prominent in the caudal parts of the putamen¹⁵. [18F]DOPA uptake correlates with clinical disease severity and with disease progression, with 8–9% annual decline in uptake rate constant in the putamen and 4–6% decline in caudate nucleus of clinical PD patients¹⁶.

EXAMINING DOPAMINE STORAGE IN SYNAPTIC VESICLES AND AVAILABILITY OF VMAT2

The dopamine produced at the synaptic level is stored in synaptic vesicles by the type-2 vesicular monoamine transporter (VMAT2), which is responsible for translocating monoamine neurotransmitters from the cytoplasm into vesicles. In the central nervous system, VMAT2 is expressed exclusively by monoaminergic neurons. Over 95% of striatal VMAT2 transporters are associated with dopaminergic terminals and striatal VMAT2 density is a linear function of the nigrostriatal neuron number¹⁷. PET radiotracer [11C] dihydrotetrabenazine ([11C]DTBZ) is a specific ligand of VMAT2

and is used as an in vivo marker of nigrostriatal dopaminergic system integrity. Studies with [¹¹C]DTBZ PET showed the expected pattern of decreased uptake in the corpus striatum in PD patients compared to control subjects, involving preferentially the putamen¹⁸. [¹¹C]DTBZ uptake is not affected by synaptic dopamine levels or dopaminergic agents, which makes the tracer one of the best available radioligands to examine dopaminergic system integrity .

ASSESSMENT OF AVAILABILITY OF PRESYNAPTIC DOPAMINE TRANSPORTERS

Dopamine transporters (DAT) are located in the presynaptic dopaminergic nerve terminal. Dopamine reuptake through the DAT is the primary mechanism of dopamine removal from the region of the synaptic cleft. A decrease in DAT density indicates decreased amount of presynaptic terminals that produce dopamine. Among many DAT-specific tracers used in PET and single photon emission computed tomography (SPECT) imaging, the cocaine analogs, 2âcarbomethoxy-3â-[4-[¹²³I]iodophenyl] tropane ([¹²³I] 3-CIT) and Nü-fluoropropyl-2âcarbomethoxy-3â-4-[¹²³I]iodophenylnortropane ([¹²³I]FP-CIT), are the most widely used in clinical practice due to their affinity to DAT and ability to assess decreased DAT density, which may precede clinical symptoms in PD. Therefore, the loss of nigrostriatal dopaminergic neurons in PD is mirrored by striatal DAT reductions, which can be evaluated by a variety of [¹¹C] or [¹⁸F] ligands¹⁹. Quantitative evaluation of DAT plays an important role in clinical practice and is based on measurements of the tracer binding potential, defined as the ratio of uptake in a striatal region of interest to that of a brain area devoid of specific binding (usually cerebellum or occipital lobe). PET studies evaluating DAT availability, particularly with N -(3-[¹⁸F]fluoropropyl)-2âcarbomethoxy-3â-(4-iodophenyl)nortropane ([¹⁸F]FP-CIT)¹² and 2â-carbomethoxy-3â-(4[¹⁸F]fluorophenyl) tropane ([¹⁸F]CFT) showed a reduction of striatal tracer uptake in PD patients compared to control subjects, affecting primarily the putamen and to a lesser extent the caudate nucleus. The reduction is typically more severe in the striatum contralateral to the earliest and most affected body side. Striatal DAT levels, particularly in the putamen, correlate with disease severity and decrease with PD progression^{20,21}.

METABOLIC IMAGING (REGIONAL CEREBRAL GLUCOSE METABOLISM) IN PD

In addition to loss of dopaminergic neurons, damage to subcortical structures alters the functional connectivity across brain regions in a disease-specific manner. A recent met analysis of quantitative [¹⁸F]FDG PET studies revealed widespread cortical hypometabolism in PD²². Nonquantitative [¹⁸F]FDG PET studies using normalization to the global gray matter activity consistently showed a pattern of relative cortical hypometabolism, particularly involving temporoparietal regions and increased metabolism in the putamen, globus pallidus, thalamus, brainstem, central cerebellum, white matter, and primary sensory-motor areas of PD patients^{23,24}. However, caution is necessary because relative metabolic increases may be artifactual due to normalization of the global gray matter mean, which is reduced in PD patients, as demonstrated in several quantitative [¹⁸F]FDG PET studies²⁵. Cerebral metabolic rate of glucose (CMRglc) in primary and associative visual cortex, occipitotemporal area, orbitofrontal cortex, and anterior cingulate gyrus is inversely correlated with motor impairment on clinical scales, which may

represent an effect on the cortex of dopaminergic deficits in the striatum⁵⁹. Moreover, a recent double-tracer study in early-stage PD patients using [¹²³I]FP-CIT and [¹⁸F]FDG PET demonstrated that CMRglc in premotor, dorsolateral prefrontal, anterior prefrontal, and orbitofrontal cortices, was significantly correlated with putaminal dopaminergic dysfunction, confirming the connection between striatum and frontal cortex²⁶. Formal network approaches using principal component analysis identified a PD-specific metabolic network characterized by relative hypermetabolism in the lentiform nucleus, thalamus, and brainstem, in conjunction with hypometabolism in the lateral premotor cortex and supplementary motor area . This pattern correlated with clinical impairment, was modulated by PD therapy, and discriminated PD patients from normal subjects and from atypical parkinsonian syndromes with high accuracy²⁷.

IMAGING IN PRECLINICAL PD

For every patient who presents with clinical PD there may be 10 subclinical cases with incidental brain stem Lewy body disease in the community²⁸. Subjects at risk of developing PD include carriers of genetic mutations known to be associated with parkinsonism (a-synuclein, parkin, LRRK2, glucocerebrosidase A), relatives of patients with the disorder, elderly subjects with idiopathic hyposmia, and patients with rapid-eye-movement sleep behavior disorders.

In a study conducted recently, transcranial sonography was performed in 26 LRRK2 G2019S PD patients, 50 first-degree relatives, 31 idiopathic PD (IPD) patients and 26 controls whereas DAT-SPECT was performed in 29 first-degree relatives. SN hyperechogenicity was very frequent in LRRK2-PD and aLRRK2+. Most aLRRK2 with possible surrogate markers of PD such as abnormal DAT-SPECT or RBD, also had SN hyperechogenicity, which supports that this echo feature might be a marker of PD in this asymptomatic population²⁹.

Another study collected 40 relatives of PD patients with idiopathic hyposmia after screening 400 subjects for hyposmia and, with 123I-b-CIT SPECT, found that 7 of these showed reduced striatal DAT binding³⁰. Four of these 7 subsequently converted to clinical PD over a 2 year period. Patients with idiopathic rapid-eye-movement sleep behavior disorder are at high risk of developing parkinsonism or dementia. Using 123I-IPT SPECT, another study concluded reduced striatal DAT binding in all 5 of their patients with idiopathic rapid-eye-movement sleep behavior disorder³¹. A study from 2006 reported no correlation between levels of midbrain hyperechogenicity in PD and reductions in striatal DAT binding measured with 99mTRODAT SPECT. This ûnding again suggests that transcranial sonography is detecting nondopaminergic pathology present in PD such as midbrain iron deposition³².

A simplified algorithm presented in the figure given below summarizes the role of structural and functional imaging for diagnosing and managing different parkinsonian syndromes.

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