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Positron emission tomography in premotor Parkinson's disease

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Abstract

Functional imaging can be used to detect preclinical evidence of dopamine deficiency in people deemed to be at increased risk of Parkinson's disease (PD) based on genetic or environmental risk, or because they have clinical features such as REM sleep behaviour disorder that may be a harbinger of PD. Positron emission tomography (PET) using [^{11}C]dihydrotetrabenazine to label the vesicular monoamine transporter type 2 (VMAT2), a variety of ^{11}C- or ^{18}F-labeled ligands for the membrane dopamine transporter (DAT), or 6-[^{18}F]fluoro-L-dopa (FD), which assesses uptake and decarboxylation of levodopa as well as vesicular storage of radiolabeled dopamine, can all be used, and all provide comparable, but somewhat different information. DAT binding using either PET or SPECT appears to be the most sensitive marker of dopamine denervation, while FD uptake is subject to compensatory upregulation and its reduction may more closely herald the onset of clinical disease. Alterations in glucose metabolism and in dopamine release also occur in the asymptomatic hemisphere of subjects with unilateral PD. An interesting potential application of PET is the determination of non-dopaminergic abnormalities that correlate with the presence of clinically apparent pre-motor symptoms of PD.

Keywords: Positron emission tomography; Dopamine; L-aromatic amino acid decarboxylase; Dopamine transporter (DAT); Vesicular monoamine transporter type 2 (VMAT2); Preclinical detection; Inherited Parkinson's; Olfaction; REM sleep behaviour disorder

1. Introduction

Functional imaging of premotor Parkinson's disease (PD) can essentially mean two different things: (1) the detection of preclinical abnormalities of nigrostriatal dopamine projections; (2) the detection of changes in brain circuitry that occur prior to the loss of midbrain dopamine neurons. While the latter definition, which would imply a mechanism to assess the provocative hypothesis put forward by Braak [1], is a fascinating potential use of positron emission tomography (PET), there is to date minimal literature surrounding its use, thus the bulk of this review will focus on the preclinical detection of changes in the dopamine system.

2. Detection of preclinical dopamine deficiency

In the absence of therapies with documented neuroprotective capacity, there is limited enthusiasm for detecting preclinical PD for purely diagnostic purposes. As newer treatments become available, this may change. However, preclinical detection in populations with increased risk of developing PD may be of great value for at least two other reasons: (1) the study of such individuals represents an extraordinary opportunity to study the natural history of PD at the time when changes are occurring most rapidly, and to study the compensatory changes that occur during this crucial phase; (2) the detection of preclinical abnormalities in individuals with genetic forms of PD may help localization and ultimate identification of previously unidentified gene defects.

There are at least five different approaches to detecting the scintigraphic changes typical of PD, three of which assess different aspects of the integrity of the dopamine neuron – the density of vesicular monoamine (VMAT2, labeled with [^{11}C]dihydrotetrabenazine; DTBZ) or plasmalemmal dopamine (DAT, labeled with a variety of [^{11}C] or [^{18}F] ligands) transporters, or the capacity to take up radiolabeled levodopa (6-[^{18}F]fluoro-L-dopa; FD), convert it to dopamine and store it in synaptic vesicles. The other approaches are somewhat less direct and include the use of a low-affinity ligand for the dopamine D2 receptor such as [^{11}C]raclopride to detect changes in dopamine release, or to study changes in the profile of metabolic activity or cerebral blood flow.

As the symptoms of PD are thought not to develop until there is a depletion of at least 80% of striatal dopamine (or 50% of the nigral dopamine neurons), any of the ligands

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used to assess presynaptic integrity will in most cases reliably detect dopamine denervation. The exception to this is the phenomenon of so-called Scans Without Evidence of Dopamine Deficiency (SWEDD), known to affect 10–15% of studies performed in subjects with very early disease participating in trials of neuroprotective therapy. Most of these subjects probably represented misdiagnosed cases of essential tremor, but a small proportion may indeed have had PD [2]. In these cases, the reasons for normal scans are less apparent, but may include technical issues. These exceptions notwithstanding, the three ligands behave in a comparable fashion, but there are important differences. VMAT2 and DAT ligands as well as FD all demonstrate an asymmetric reduction of radioactivity, with a rostrocaudal gradient of activity such that the caudate nucleus is relatively preserved while there is a progressive reduction of uptake going from anterior to posterior putamen. However, DAT binding appears to be the most sensitive marker of early disease, with greater reductions in early disease compared to DTBZ or FD. This possibly represents a combination of reduced DAT binding sites with loss of dopamine nerve terminals as well as downregulation of DAT in surviving terminals [3]. In contrast, FD uptake, while still abnormal, is not quite as severely affected as DTBZ or DAT binding in early disease, possibly reflecting compensatory upregulation of decarboxylase activity [3]. Although FD uptake may be a less sensitive metric of nerve terminal loss, FD uptake is known to be reduced in asymptomatic twins [4,5] and in asymptomatic subjects exposed to the nigral toxin MPTP [6].

While post-synaptic dopamine receptors are preserved or slightly increased in early, untreated PD, a small reduction in [^{11}C]raclopride binding has been demonstrated in monkeys with mild nigral dopamine cell loss induced by MPTP [7], likely reflecting selective loss of D2-like autoreceptors located on presynaptic dopamine nerve terminals. Increases in striatal dopamine release can be detected by a reduction in [^{11}C]raclopride binding. One means of inducing dopamine release is with repetitive transcranial magnetic stimulation (rTMS). In patients with unilateral PD, the anatomical distribution of putaminal dopamine release is preserved in the asymptomatic striatum following rTMS (and the magnitude is if anything greater than that seen in normal individuals, possibly reflecting increased dopamine turnover). In contrast, dopamine release is reduced in magnitude, but the anatomical spread is greater in the symptomatic striatum, suggesting loss of functional segregation of corticostriatal inputs in PD [8].

Another approach is the study of patterns or networks of regional activation, using measures of either cerebral blood flow or glucose metabolism and a principal components analysis. PD is characterized by increased metabolism in subcortical nuclei such as basal ganglia and thalamus as well as pons, cerebellum and primary motor cortex, with concurrent decreases in premotor cortex, supplementary motor area and posterior parietal cortex. Although such changes have not to date been reported in presymptomatic individuals, extrapolation suggests that this pattern is likely present approximately 5 years prior to clinical disease onset [9] and indeed, similar changes are seen in the asymptomatic hemisphere of individuals with unilateral disease [10], akin to findings reported using DAT ligands and single photon emission computed tomography (SPECT) or PET.

While asymptomatic imaging changes may occasionally be detected in individuals where they are truly unexpected, the most fruitful population in which to study preclinical disease is one in which there is a substantially elevated risk of PD. Calne et al. demonstrated such changes using FD PET in subjects exposed to MPTP, but in whom there were no symptoms or clinical signs [6]. Repeat study of these individuals showed progressive loss of FD uptake over time, as well as new clinical signs of disease, despite lack of continued exposure to the toxin [11]. The most obvious situation, however, is the study of families with genetic PD. The commonest of the dominantly inherited forms of PD is that due to mutation of the LRRK2 gene. Adams et al. studied two kindreds, families A and D, with Y1699C and R1441C substitutions, respectively, using a combination of [^{11}C]DTBZ, [^{11}C]*d-threo*-methylphenidate (MP; a DAT ligand) and FD [12]. In affected members of both families, the pattern of tracer uptake was identical to that seen in sporadic PD, with asymmetry and a rostrocaudal gradient. VMAT2 and DAT binding were affected more than FD uptake, in keeping with our earlier report of compensatory changes in early sporadic PD [3]. In the original study there was one asymptomatic individual who had abnormal DAT and VMAT2 binding but FD uptake within normal limits. This individual was studied 4 years later, by which time he had gone on to develop early clinical signs of PD and FD uptake was reduced. In follow-up studies conducted in these and other kindreds, we found that several individuals who were normal at the time of the original study had gone on to develop asymptomatic abnormalities on imaging within 4 years of follow-up [13]. However, in all cases, DAT (and in some cases VMAT2) binding were reduced to a greater extent than FD uptake and in no case were there clinical abnormalities unless FD uptake was reduced below the control range. It therefore appears that FD uptake may be somewhat less sensitive to asymptomatic disease than either VMAT2 or DAT binding, but this may reflect compensatory upregulation of decarboxylase activity. Once this compensation becomes inadequate, symptoms develop. It would also appear based on these studies that DAT binding is reduced to a greater extent than VMAT2 binding, also in keeping with compensatory downregulation of the DAT.

In recessively inherited PD, findings are somewhat different. In subjects with established disease, there is less sparing of the caudate nucleus compared to sporadic PD, in contrast to dominantly inherited PD [14,15]. Although earlier reports