IS MOLECULAR IMAGING USEFUL IN DIAGNOSING PARKINSON DISEASE – NO

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Introduction: 20th century marked the development of structural imaging of the disease. Significant advances have been made in the 21st century in molecular imaging and helps us to sub classify clinical disease and thus guide management. Although the clinical utility of all these techniques is not fully understood the applications are growing continuously in Parkinsonism and other neuro behavioural syndromes.

Molecular Imaging: Several dopamine-related imaging agents have been developed to assess the integrity of dopaminergic neurons using single photon emission computed tomography (SPECT) or positron emission tomography (PET).

These radioligands image either

- presynaptic targets –
  - dopamine transporter (DAT scan),
  - vesicular monoamine transporter, or
  - dopa decarboxylase activity (reflecting dopamine synthesis) or
- postsynaptic D2 dopamine receptors

[18F]-Dopa PET study

18F-L-6-fluoro-3,4-dihydroxyphenylalanine (18F-DOPA) is a representative radioligand for dopamine synthesis and measures changes in aromatic L-amino decarboxylase (AADC) activity, which is dependent on the availability of striatal dopaminergic nerve terminals and is proportional to the number of dopamine neurons in the substantia nigra *(1)*.

18F-DOPA uptake is not a direct measure of nigral cell count (2). At disease onset, false negative cases have been reported due to the compensatory upregulation of AADC in preserved dopaminergic terminals, which implies that at this stage of the disease, [18F]-Dopa underestimates the degenerative process (Ribeiro et al., 2002).

DAT imaging: The dopamine transporter (DAT) controls the intensity and duration of dopaminergic neurotransmission by rapid reuptake of dopamine into presynaptic terminal (3–5). DAT density correlates with the density of dopaminergic neurons and is used as an imaging biomarker for diagnosing PD.

DAT imaging is not necessary in clinically definite PD patients. DAT imaging is currently not recommended as a stand-alone diagnostic tool (7). It does not help to differentiate PD from atypical Parkinsonian syndrome (APS) (e.g., multiple-system atrophy, progressive supranuclear palsy and corticobasal degeneration). Both PD and APS have presynaptic dopaminergic degeneration and demonstrate decreased striatal uptake on DAT imaging. Postsynaptic dopaminergic imaging needs to be added to increase diagnostic accuracy (8). Postsynaptic D2 receptor binding is normal or increased in PD whereas it is decreased in APS (36). 18F-FDG PET has been also used to distinguish PD from APS using their different metabolic patterns (9-11).

Whether DAT imaging is useful in the assessment of treatment response, monitoring of disease progression and early diagnosis of PD in the premotor stage is still in its research phase.

There is a correlation with bradykinesia but not with tremor, thus suggesting that the origin of tremors is beyond the DAT system.

In a study on 32 PD patients using [123I] β-CIT (DAT scan), it was found that although striatal uptake was correlated with clinical severity, the annual percentage loss of striatal uptake did not correlate with the annual loss in measurements of clinical function (6).

Postsynaptic D2 Receptor Imaging

Dopamine receptors can be studied using a variety of C-11- or F-18-labeled ligands for the D2 receptor (some 123I-labeled ligands are available for SPECT as well), with fewer options available for the D1 receptor. Some D2 receptor ligands are susceptible to competition from endogenous dopamine or by pharmacological agents that bind to dopamine receptors. On the one hand, this can lead to problems of interpretation because differences in binding could potentially reflect alterations in receptor occupancy

by endogenous neurotransmitter rather than changes in receptor expression. However, this property may also be extremely useful for estimating changes in dopamine release in response to a variety of behavioral (Monchi et al., 2006), pharmacological (Piccini et al., 2003; Tedroff et al., 1996), or physical (Strafella et al., 2003) interventions.
The distinction between CBD and other Parkinsonian syndromes by means of DAT and Postsynaptic D2 receptor imaging is limited (12).

Image Artifacts

1.Patient motion can result in markedly impaired image spatial resolution, potentially leading to inaccurate image interpretation. This pitfall may be especially relevant for patients with movement disorders who may not be able to remain motionless voluntarily.
2. Equally important is to ensure symmetrical patient positioning, and in the case of SPECT-CT, proper alignment between the radionuclide and CT images.
For example, misalignment associated with lateral tilting of the head can produce apparent asymmetry of striatal uptake that may simulate an abnormal study.

Potential Effects of Drugs on Dopaminergic Imaging: Cocaine, amphetamines, modafinil, certain antidepressants (mazindol, bupropion, radafaxine), adrenergic agents (phenylephrine, norepinephrine), and the anticholinergic agent benzatropine, and ideally should be discontinued for at least 5 half-lives (typically 7 days) before the study.

Contraindications: Patients with known hypersensitivity to the active substance or other constituents of the radiopharmaceutical preparation and Administration to pregnant or paediatric patients
Nursing women may undergo dopamine transporter scintigraphy provided that breast feeding is interrupted and expressed milk discarded for a reasonable period of time, typically 1 to 6 days, similar to other containing radiopharmaceuticals.

Conclusion:

- False negative study with 18F- Dopa study.
- Difficulty in differentiating between PD and Parkinsonsonian syndromes with DAT imaging.
- Discordance between PET or SPECT findings and clinical observations.
- Relatively low spatial resolution.
- Potential effects of drugs.
- Image artifacts (Movements/ Head position).
- Contraindications.
- PET cyclotron or generator needed.
- Cost and availability factors.

***References*:**

1.Snow BJ, Tooyama I, McGeer EG. Human positron emission tomographic (fluorine-18)fluorodopa studies correlate with dopamine cell counts and levels. Ann Neurol 1993;34:324–330.
2.Ravina B, Eidelberg D, Ahlskog JE, et al. The role of radiotracer imaging in Parkinson disease. Neurology. 2005;64:208–215.
3. Jaber M, Jones S, Giros B, Caron MG. The dopamine transporter: a crucial component regulating dopamine transmission. Mov Disord. 1997;12:629–633.
4. Amara SG, Kuhar MJ. Neurotransmitter transporters: recent progress. Annu Rev Neurosci. 1993;16:73–93.
5. Giros B, Caron MG. Molecular characterization of the dopamine transporter. Trends Pharmacol Sci. 1993;14:43–49.
6 . Marek K, Innis R, van Dyck C, et al. [123I]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression - Neurology. 2001;57(11):2089-94
7.GE Healthcare. DaTSCANTM (ioflupane I-123 injection) briefing document: peripheral and central nervous system drugs advisory committee meeting. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM186404. pdf. Accessed October 31, 2012.
8. Mo SJ, Linder J, Forsgren L, Larsson A, Johansson L, Riklund K. Pre- and postsynaptic dopamine SPECT in the early phase of idiopathic parkinsonism:

a population-based study. Eur J Nucl Med Mol Imaging. 2010;37:2154–
2164.
9. Eckert T, Tang C, Ma Y, et al. Abnormal metabolic networks in atypical parkinsonism. Mov Disord. 2008;23:727–733.
10. Juh R, Kim J, Moon D, Choe B, Suh T. Different metabolic patterns analysis of Parkinsonism on the 18F-FDG PET. Eur J Radiol. 2004;51:223–233.
11. Kwon KY, Choi CG, Kim JS, Lee MC, Chung SJ. Diagnostic value of brain MRI and 18F-FDG PET in the differentiation of Parkinsonian-type multiple system atrophy from Parkinson's disease. Eur J Neurol. 2008;15:1043–1049.
12. Schreckenberger M, Hagele S, Siessmeier T, et al. The dopamine D2 receptor ligand 18 desmethoxyfallypride: an appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism. Eur J Nucl Med Mol Imaging. 2004;31(8):1128-35.

Sudy report - regarding DAT IMAGING:

123I-FP-CIT SPECT has been successfully used to detect the loss of dopaminergic nigrostriatal neurons in Parkinson's disease at an early stage. But the results reported were controversial.
Tissingh et al. reported that striatal 123I-FP-CIT uptake is markedly decreased in PD, more in the putamen than in the caudate nucleus, and the mean reduction in the putamen and caudate nucleus was 57% and 29% of the control mean, respectively. However, no significant correlations were found between striatal 123I-FP-CIT binding ratios and disease severity.
Spiegel et al. found that the striatal FP-CIT binding correlated significantly with the motor part of the unified Parkinson's disease rating scale (UPDRS) but not with age, disease duration, or gender. Another study indicated that in patients with PD, the striatum, caudate, and putamen uptake was correlated with disease severity assessed by UPDRS and duration of disease [36]. More studies are needed to confirm these findings.