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Introduction

It is an exciting time to be in the field of molecular imaging of the brain with clinical applications in neurodegenerative disorders set to soar in the foreseeable future. An exciting development in the area of molecular imaging has been the development of β -amyloid radiopharmaceuticals that can detect Alzheimer's disease before the development of dementia and reliably distinguish Alzheimer's disease from frontotemporal dementia.

The Brain Imaging Council (BIC) honored Dr. Chester Mathis from the University of Pittsburgh with the 2009 Kuhl-Lassen award for his pioneering work in the development of β -amyloid imaging. Several companies have committed to the development of an ^{18}F β -amyloid ligand with phase II and III trials under way. Agents under development include florbetapir from Avid Radiopharmaceuticals, florbetaben from Bayer AG and flutemetamol from General Electric.

Another significant development is that a dopamine transporter radioligand may become available in the U.S. for a proposed indication of the detection of loss of functional nigrostriatal dopaminergic neurons by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration. Presynaptic nigrostriatal dopaminergic denervation is a key pathobiological mechanism of Parkinson's disease. DaTSCAN™ (Ioflupane, ^{123}I FP-CIT, GE Healthcare) has been available in Europe since 2000 and has been used in more than 200,000 patients in 32 countries. It is expected that dopamine transporter imaging will fill a vacant clinical niche in neuro-nuclear medicine in the U.S.

Nicolaas I. Bohnen, MD, PhD

Dopamine Transporter SPECT Imaging

Background

^{123}I -FP-CIT (N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl) nortropane, ioflupane, distributed by General Electric Healthcare) is an agent for dopamine transporter (DaT) SPECT imaging that is currently under consideration for FDA approval and may soon become available on the U.S. market. In Europe, this agent has been approved since 2000 and several hundreds of thousands of patients have been scanned. It proved to be

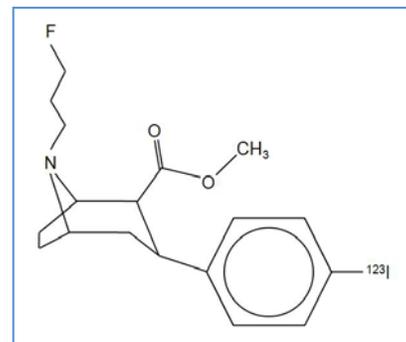


Figure 1: ^{123}I -FP-CIT

safe, reliable and very helpful in the differential diagnosis of movement disorders and dementia.

^{123}I -FP-CIT is a cocaine analogue and has high affinity and relatively good selectivity for the dopamine transporter and can be used to visualize nigrostriatal dopaminergic nerve terminals. The most intense signal is seen at the level of the putamen and caudate nucleus. The dopamine transporters are located at the presynaptic side (see Figure 2). They transport dopamine out of the synaptic cleft, back into the presynaptic nerve endings for either re-use or degradation.

Nigrostriatal dopaminergic denervation is a key pathobiological event in Par-

kinson's disease (PD) and related parkinsonian disorders, and in dementia with Lewy bodies (DLB). The lower number of

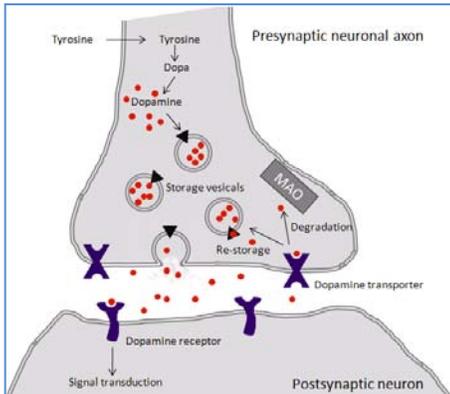


Figure 2: Dopaminergic Nerve Terminal nigrostriatal nerve terminals in PD and DLB results in decreased striatal signal on DaT imaging. Therefore, FP-CIT can be used in the differential diagnosis of specific movement disorders and dementias.

Post mortem studies showed that in vivo diagnosis based on clinical criteria can be difficult, even in specialized centers, and especially in the earliest stages of disease when clinical symptoms can be subtle. However, accurate diagnosis is important for treatment and estimating prognosis. Structural imaging with CT or MRI usually is of little aid. Imaging dopamine transporters gives specific neurobiological information and it has even been suggested that it should be incorporated in the definition of Parkinson's disease.

Decreased DaT binding is an early feature in degenerative disease of the presynaptic neurons. Degeneration of these neurons leads to a lower density of dopamine transporters in the striatum. This decrease might even be more prominent due to compensatory downregulation of dopamine transporters in an attempt to increase synaptic dopamine concentration. Moreover, Parkinson symptoms typically only become apparent after at least 50% of nigrostriatal nerve terminals are lost. Thus, DaT imaging is excellent for early diagnosis of Parkinson's disease and the degree of reduction in DaT binding is re-

lated to the clinical stage and severity of Parkinson's disease. DaT SPECT can be used to rule out degeneration of the presynaptic neurons in patients with essential tremor, psychogenic parkinsonism and neuroleptic drug induced parkinsonism.

It should be noted that presynaptic nigrostriatal dopaminergic degeneration can be seen not only in Parkinson's disease but also in other parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, where reduced striatal DaT binding can also be seen. Unfortunately, although the pattern of DaT binding sometimes tends to be somewhat different, there is large overlap in striatal DaT imaging findings between these entities, which means that, on its own, ¹²³I-FP-CIT imaging is unable to discriminate between these syndromes. Imaging of the postsynaptic dopamine receptors may have utility in distinguishing idiopathic Parkinson's disease where these receptors may be upregulated, at least in early stages of disease, whereas there is loss of post-synaptic dopamine receptors in the atypical parkinsonian disorders. However, postsynaptic dopamine receptor imaging may not distinguish these atypical parkinsonian disorders from each other. In this context, FDG PET may be of use to differentiate.

Another important indication is the differentiation of dementia with Lewy bodies from other dementias. This is important because patients with Lewy body disease respond better to therapy with acetylcholine esterase inhibitors, and may suffer from severe side effects during treatment with neuroleptic drugs. Furthermore prognosis is different. In dementia with Lewy bodies, DaT binding is reduced, whereas in most other dementias (of course with the exception of

dementia associated with Parkinson's disease) DaT binding is normal.

Possible Indications for ¹²³I-FP-CIT imaging

- Detection of loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndromes
- Early detection of Parkinson's disease
- Assessment of disease severity and progression
- Differentiation of essential tremor, psychogenic parkinsonism, or neuroleptic induced parkinsonism from parkinsonian syndromes (Parkinson's disease, multiple system atrophy, progressive supranuclear palsy)
- Differentiation of dementia with Lewy bodies from other dementias

Technical Aspects

Typically 185 MBq of ¹²³I-FP-CIT is injected intravenously. It is cleared rapidly from the blood. No important differences are to be expected in patients with impaired renal or hepatic function. The effective dose is 6 mSv, and the organs receiving the largest dose are the basal ganglia (0.3 mSv) and the lungs/liver (0.1 mSv). The only contra-indication is pregnancy. Breast feeding should be interrupted for at least 24 hours after injection of the isotope.

Anti-parkinsonian medications do not significantly interfere and therefore do not need to be discontinued. Of course cocaine and related substances (e.g. methyl-

phenidate, fentanyl, ketamine) may interfere with the scan and should be discontinued (See Booij J et al. *Eur J Nucl Med Mol Im-*



Figure 3: Multiple intensity projection of ¹²³I-FP-CIT SPECT: Normal (left) and severely abnormal (right). Note also the normal uptake in the parotid glands.

aging 2008; 35: 424-38 for an extensive list of interfering medications).

Three to six hours after injection, SPECT images are acquired on a dual- (or more) head gamma camera. On a dual-head camera this typically takes 30-45 minutes. The patient should be in a comfortable position and the head and shoulders may be fixated to avoid movement during acquisition. Fixating the shoulders might also reduce the radius of the detector orbit, thus enhancing image quality. Reconstruction is straightforward. A detailed procedure guideline is freely downloadable from the European Association of Nuclear Medicine's website (https://www.eanm.org/scientific_info/gui_delines/gl_neuro_spet_trans.pdf).

Image Interpretation

¹²³I-FP-CIT imaging shows the distribution of the dopamine transporters in the striatum. Ideally structural scans should be present for correlation (especially in case of severe changes due to infarction or enlargement of the ventricles), although they are usually not necessary for interpretation of the DaT image.

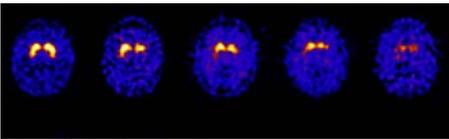


Figure 4: Examples of ¹²³I-FP-CIT images.

Images are visually assessed, preferably after reorientation of the head according to the orbitomeatal plane to avoid false impressions of asymmetry due to tilting of the head. The images should be checked for motion artifacts, which may cause blurring, asymmetry and a decrease of the target to background ratio, but this easily recognized.

In a normal scan, the striatum is clearly visible as symmetric, comma-shaped regions, with both the caudate and putamen showing a high intensity compared to the background. With increasing age, some decline in the target to back-

ground is allowed (typically some 5% decrease in ratio per decade) but it should remain high. There is also some accumulation of activity in the parotid glands, which are often in the field of view.

In early Parkinson's disease, there is usually an asymmetrical pattern of reduced DaT binding starting in the dorsal putamen contralateral to the clinically most symptomatic body side, gradually progressing anteriorly and ventrally and towards the other side as the disease becomes more severe. Activity in the caudate nucleus is relatively preserved in early disease but will also decline with advancing disease. In the atypical parkinsonian syndromes, there usually will be a more symmetrical decrease in DaT binding. However, there is too much overlap to reliably differentiate between these parkinsonian syndromes.

In dementia with Lewy bodies, DaT binding is reduced, typically with bilateral loss of DAT binding, mainly in the putamen but also in the caudate and generally with less asymmetry than in Parkinson's disease.

Many specialized centers also use semi-quantitative assessments in which specific binding ratios are calculated. In some studies, even only semi-quantitative outcome measures are used. These ratios are calculated by subtracting background DaT binding (usually the occipital cortex or cerebellum is used as a reference area) from DaT binding in a particular region of interest (e.g. caudate nucleus, putamen, or the striatum as a whole) and dividing by the reference background activity.

These ratios can be compared to values of a normal reference population. However, quantification is influenced by the scanning protocol, the camera used (there are even differences between cameras of the same brand and type), the reconstruction algorithms, and the observer-dependent placement of volumes-of-interest (especially in inexperienced observers), etc. Therefore it is difficult to compare results with those normal values of another center. However, centers can be cross-validated and calibrated but

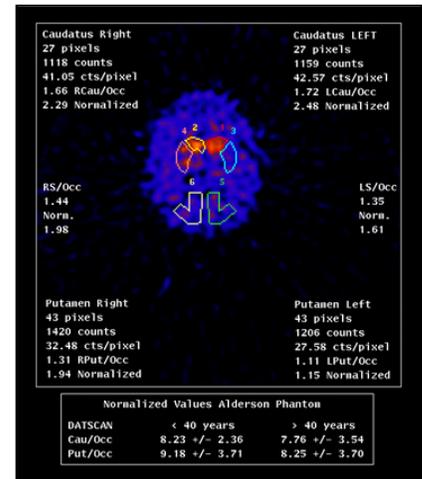


Figure 5: Quantitative analysis in patient with severe Parkinson's disease

this is troublesome and requires the use of a travelling phantom. Although quantification may have some advantages, especially for research purposes or in case of very subtle changes, it usually is not necessary because the decrease in DaT binding is clearly visible even in the early stages of idiopathic Parkinson's disease.

Conclusion

Dopamine transporter imaging with ¹²³I-FP-CIT is currently under consideration for FDA approval. It is a robust and simple technique that can detect Parkinson's disease, even in very early stages, and can differentiate parkinsonian syndromes from essential tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism, but when used by itself cannot differentiate between the different atypical parkinsonian syndromes. Furthermore, DaT imaging may be used to differentiate dementia with Lewy bodies from other types of dementia, such as prototypical Alzheimer's disease.

*Marcel JR Janssen, MD
Radboud University Nijmegen
Medical Centre
Nijmegen, The Netherlands*

Getting More Clinically Useful Information out of Dynamic Neuroligand Imaging in the Management of Neurodegenerative Disorders

There are three general strategies to use functional neuroimaging to aid the clinical diagnosis of a patient with neurodegenerative disorders, such as dementia. The first and most commonly applied strategy is to assess global neuronal function by imaging the biological consequences of cell death and/or synaptic dysfunction on the basis of regional cerebral glucose metabolism or blood flow (rCBF).

FDG PET or rCBF SPECT are examples of this strategy and are the only radiotracer imaging methods clinically approved for the differential diagnosis of dementia in the U.S. at the present time.

The topographic pattern of decreased cerebral metabolic or perfusion activity in conjunction with areas of normal or relatively preserved activity allows sensitive and relatively specific diagnostic assessment of the major neurodegenerative disorders, including Alzheimer's disease, frontotemporal dementia and dementia with Lewy bodies.

The second diagnostic imaging strategy is to apply a radiopharmaceutical that binds to a disease-specific neurochemical abnormality. Ligands that visualize the presynaptic dopaminergic nerve terminal are an example of this strategy. These ligands demonstrate the well-known nigrostriatal loss in Parkinson disease and may also aid the differential diagnosis of dementia with Lewy bodies from prototypical Alzheimer's disease.

The third and very promising imaging strategy is to use a radiolabel that is specific for a particular neuropathological substrate of a dementia syndrome. For example, β -amyloid binding ligands can be

used to image amyloid plaques in Alzheimer's disease.

Possible future clinical applications of dopaminergic and β -amyloid imaging are illustrated in the diagnostic work-up of a 72-year-old male with treatment non-responsive parkinsonian motor symptoms and dementia where normal ^{11}C -DTBZ (Figure 1A) and negative normal ^{11}C -PIB (Figure 1B) PET scans helped to exclude nigrostriatal dopaminergic denervation and amyloidopathy, respectively.

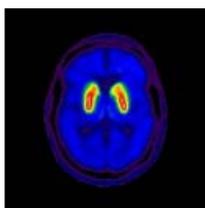


Figure 1A:
 ^{11}C -DTBZ scan

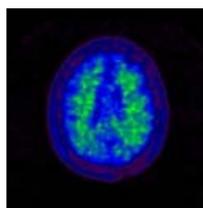


Figure 1B:
 ^{11}C -PIB scan

Recent correlative FDG PET and β -amyloid imaging have shown, however, that sometimes FDG patterns thought to be specific for non-Alzheimer dementia still may represent the presence of amyloidopathy. For example, Alzheimer's disease may sometimes present as a predominant frontal hypometabolic variant.

There is also evidence that patients clinically diagnosed with dementia with Lewy bodies may not only have nigrostriatal dopaminergic denervation, but also a higher load of co-morbid amyloidopathy.

These observations suggest that traditional diagnosis based on FDG PET or rCBF SPECT may have limitations to explain the full pattern of neurodegenerations in the work-up of a patient with dementia. Several companies are now in the process of performing clinical studies of radiopharmaceuticals to detect cerebral β -amyloid deposits or the presence of nigrostriatal dopaminergic denervation.

A novel strategy that is now considered is to get FDA approval for an indication to detect a pathobiological process, such as

amyloidopathy, rather than a disease-specific indication. Such a new FDA approval process would open the way to diagnose the presence of specific pathologies in the brain that potentially would be amenable to personalized therapy rather than an exclusive diagnostic process per se.

However, these ligands may have limitations when used in the clinical context of mixed or overlapping pathologies, such as co-morbid presence of Alzheimer pathology in Parkinson disease with dementia.

Therefore, the diagnosis of a neurodegenerative disorder in the future probably will depend on the integration of different sources of information, including development of new non-imaging biomarkers. Imaging-wise, a combination of above-mentioned strategies rather than a single one will probably be needed to better meet the future clinician's need at a time when not only more and specific treatment strategies are emerging, but there is also a strong patient's need to be informed about prognosis and monitoring of outcome of such novel treatment strategies.

Thus, the advantage of global neuronal "whole brain" metabolic or perfusion information is that it may provide information beyond the presence of a specific pathology and may also have implications for prognostic outcome.

In this respect, it could be used to monitor global cerebral outcome effects of specific anti-dementia therapies analogous to the way FDG PET is used in oncology to assess efficacy of heterogeneous anti-cancer therapies.

A unique advantage of dynamic PET imaging is that for some tracers, such as ^{11}C -DTBZ, the single-pass extraction fraction across the blood-brain barrier at the cortical level is high and hence the transport rate K_1 provides a good index of rCBF (Figure 2).

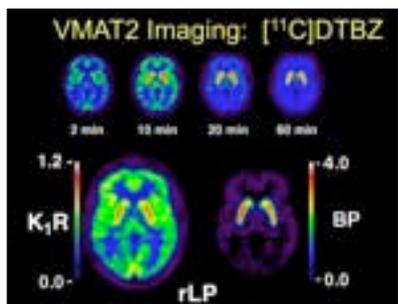


Figure 2: Dynamic DTBZ PET Imaging

The strong coupling between cerebral blood flow and metabolism is well known, as pointed out by Sherrington and Roy over a century ago. Previous work at the University of Michigan by Koeppe *et al.* has shown that the K_1 images obtained when performing ^{11}C -DTBZ PET images provide near identical information about cortical function as FDG glucose metabolic PET images in patients with Alzheimer's disease, dementia with Lewy bodies, or frontotemporal dementia (see Figure 3).

Although there are some discrepancies in the striatum, where relatively high specific binding of DTBZ may contaminate the K_1 values, this region is typically not used for analysis of regional cortical perfusion patterns in dementia. These results indicate that regional cortical perfusion maps with the K_1 parameter of DTBZ PET imaging provides data nearly equivalent to FDG PET studies. These data show also that dynamic ^{11}C -DTBZ PET imaging can provide two important biomarkers, one related to the dopamine neurotransmitter system, and the other related to global cortical neuronal function. For example, a single dynamic neuroimaging session has been found to allow a more confident differentiation from dementia with Lewy bodies from both Parkinson disease and Alzheimer's disease (Koeppe *et al. Alzheimers Dement* 2008;4, Suppl 1: S67-S76). A similar approach was also used by Van Laere and colleagues (*J Nucl Med* 2010;51:588-595) who used information from striatal dopamine receptor type 2

binding of ^{11}C -Raclopride and cerebral influx information and found that combined information from these two imaging func-

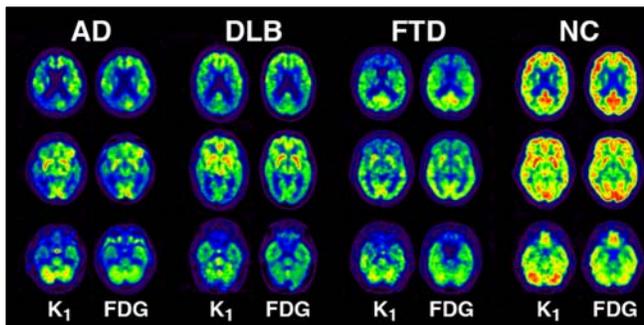


Figure 3: Parametric images of DTBZ K_1 and FDG uptake obtained in clinically diagnosed frontotemporal dementia (FTD), Alzheimer's disease (AD), dementia with Lewy bodies (DLB) subjects, and in a normal control (NC). There is excellent correspondence between DTBZ K_1 and FDG patterns in cortical regions.

tions improved early differentiation between multiple system atrophy from idiopathic Parkinson disease.

Nicolaas I. Bohnen, MD, PhD

Robert A. Koeppe, PhD

University of Michigan, Ann Arbor, MI

Epilepsy Imaging in the Era of Quantitative Analysis: The Freeware-Software Challenge

Surgical resection of a correctly localized seizure focus in patients with intractable epilepsy has been shown to be a great success. Post-surgical outcomes are more favorable for temporal lobe rather than for neocortical epilepsy. However in both cases—more in the latter—imaging has provided great data to guide surgical decisions and techniques. Most recently, it has been reported that this practice is underutilized.

It requires an expert epilepsy team composed of skilled neurosurgeons, epilepsy specialists and imaging physicians in this topic. Quantitative imaging techniques have been developed and are progressively becoming user friendly, simplifying the at-

tainment of this expertise. Increasingly, computer-aided diagnostics (CAID) are used in radiology for various modalities (nuclear medicine and MRI, most commonly).

Nuclear medicine has been using many variants of CAID for many years. Various software packages have also recently entered the commercial market and increased in accuracy and flexibility of

use. Subtraction techniques of Ictal and Interictal studies have added substantial diagnostic accuracy to the localization of epileptogenic foci. Subtraction techniques have been mainly applied to regional cerebral blood flow SPECT studies using the radioligands $^{99\text{m}}\text{Tc}$ -HMPAO and $^{99\text{m}}\text{Tc}$ -ECD. Subtraction techniques can be used by itself or with added use of statistical parametric mapping (SPM) with normal database comparisons and generation of statistical scores. Various commercial semi-automated software packages are available on the market; however, several freeware programs are also available to nuclear imaging specialists. For example, the Yale group offers a free downloadable version with complete instructions on SPECT.yale.edu. The Yale group has described improved accuracy when Ictal-Interictal subtraction is compared to a normal database for expected variability in between scans (McNally KA, *et al. Epilepsia* 2005;46:1450–1464). This has been confirmed more recently by the Mayo Clinic group using a modified image analysis algorithm (Kazemi NJ, *et al. Neurology*. 2010;74:70-6). Techniques used by both groups are based on the same concept; however, some differences are to be noted in: timing of injections, tracers utilized (HMPAO for Yale and ECD for the Mayo group), differences in scanners, acquisition and reconstruction protocols, warping techniques, threshold values and SPM software analysis. These

methods are available to nuclear medicine physicians and may greatly enhance diagnostic accuracy when performing Ictal and Interictal rCBF studies in patients with epilepsy. It should be noted that if CAID is used as a primary rather than supportive tool for diagnostic and clinical purposes, the software package will need to be FDA-approved.

*Mehdi Djekidel MD
Diagnostic Radiology/
Nuclear Medicine Section
Yale University School of Medicine,
New Haven, CT*

