

Dopamine transporter SPECT imaging

Background

¹²³I-ioflupane (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropine, FP-CIT), is an agent for dopamine transporter (DaT) SPECT imaging that has recently been FDA approved and has become available on the US market. In Europe this agent has been approved since 2000 and several hundreds of thousands of patients have been scanned. It proved to be safe, reliable, and very helpful in the differential diagnosis of movement disorders and dementia.

¹²³I-ioflupane 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 pathological event in

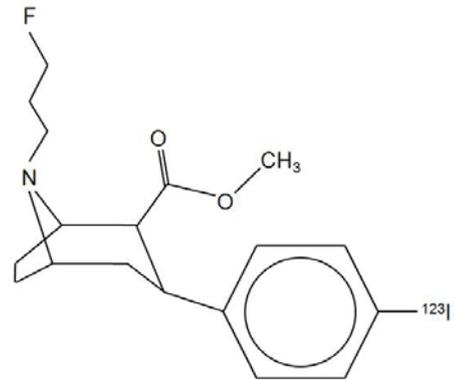


Figure 1: ¹²³I-ioflupane

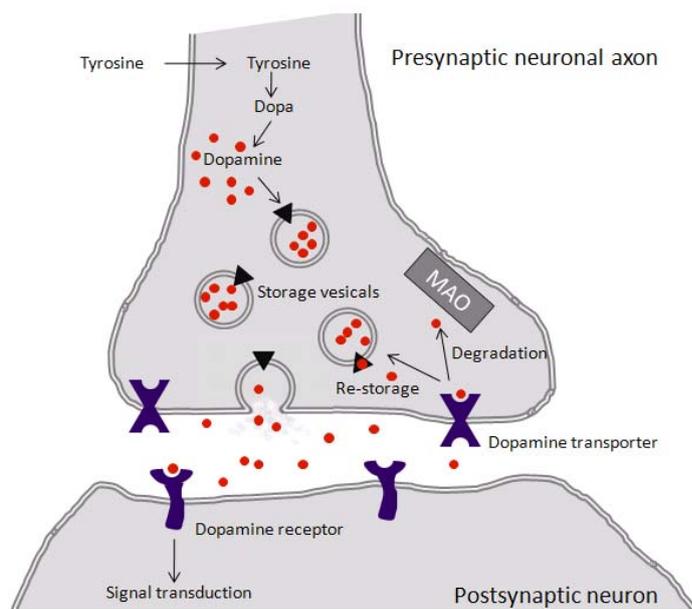


Figure 2: Dopaminergic synapse in the striatum

Parkinson's disease (PD) and related parkinsonian disorders, and in dementia with Lewy bodies (DLB). The lower number of nigrostriatal nerve terminals in PD and DLB results in decreased striatal signal on DaT imaging. Therefore, ioflupane 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. 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. 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, and corticobasal degeneration. Therefore, these syndromes also show reduced striatal DaT binding. 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, ^{123}I -ioflupane 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.

Possible Indications for ^{123}I -ioflupane imaging

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

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.

Technical aspects

Typically 185 MBq of ^{123}I -ioflupane is injected intravenously. It is cleared rapidly from the blood. To reduce exposure of the thyroid to free ^{123}I , a single 400-mg dose of potassium perchlorate or a single dose of potassium iodide oral solution or Lugol solution (equivalent to 100 mg of iodide) can be administered at least 1 h before the tracer injection, unless the patient has a known sensitivity to any of these products. Even in the absence of a blocking agent, the radiation dose to the thyroid would be low. The only contra-indications are pregnancy, the inability to cooperate with SPECT brain imaging or a known hypersensitivity to the active substance or to any of its excipients (which is rare). An iodine allergy is, however, not a contraindication to receiving this tracer. Breast feeding should be interrupted for at least 24 hours after injection of the isotope.

Anti-parkinsonian medications usually do not significantly interfere and therefore do not need to be discontinued. Of course cocaine and related substances (e.g. methylphenidate, fentanyl, ketamine) may interfere with the scan and should be discontinued (See Booij J et al. Eur J Nucl Med Mol Imaging 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 SNM website.

Image interpretation

^{123}I -ioflupane 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 3: Multiple intensity projection of ^{123}I -ioflupane SPECT: Normal (left) and severely abnormal (right). Note also the normal uptake in the parotid glands.

Images are visually assessed, preferably after reorientation of the head to avoid false impressions of asymmetry due to tilting of the head. Transverse slices should be parallel to a standard and reproducible anatomic orientation, such as the anterior commissure–posterior commissure line as used for brain MRI. The images should be checked for motion artifacts, which may cause blurring, asymmetry and a decrease of the target to background ratio, but this is 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 background is allowed (typically some 5-8% 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.

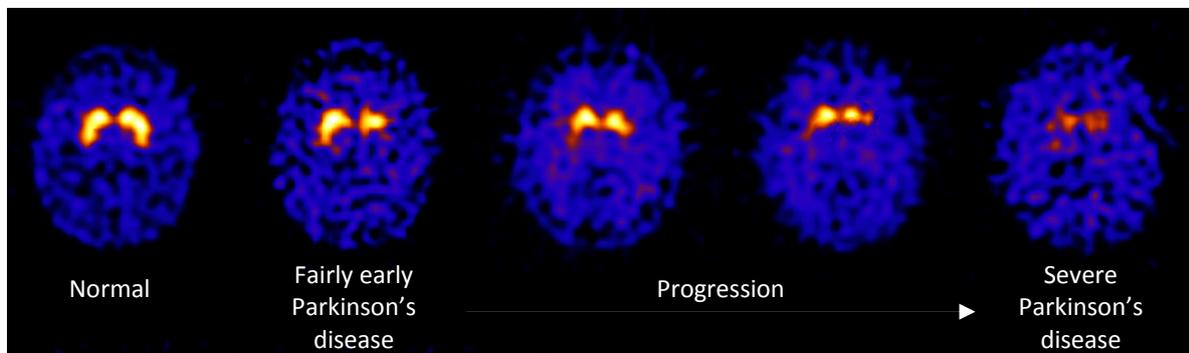
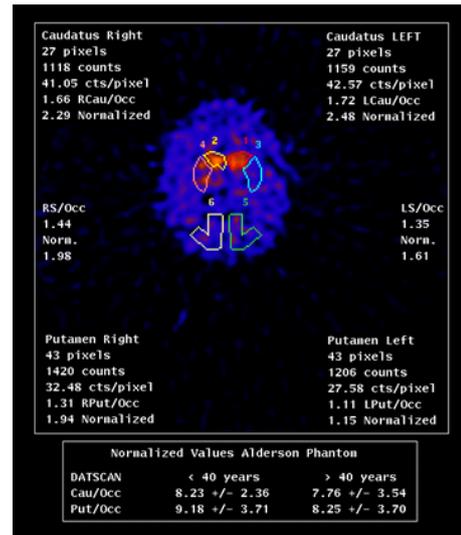


Figure 4: Examples of ^{123}I -ioflupane images.

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 ipsilaterally 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 and relatively more involvement of the caudate nucleus. 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, preferably age-matched. However, because semi-quantification is influenced by many factors (scanning protocol, camera, reconstruction algorithms, placement of regions/volumes-of-interest, etc.) there is no universal cutoff value for normal vs. abnormal. Each site needs to establish its own reference range by scanning a population of healthy controls or needs to calibrate its procedure with another center that has a reference database. The latter can be done using an anthropomorphic phantom filled with different concentrations of activity. 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 ^{123}I -ioflupane has recently been FDA approved. It can differentiate presynaptic parkinsonian syndromes (Parkinson's disease, multiple-system atrophy, coticobasal degeneration and progressive supranuclear palsy) from essential tremor, neuroleptic induced parkinsonism and psychogenic parkinsonism, but when used by itself it can not differentiate between these presynaptic parkinsonian syndromes. Furthermore, ^{123}I -ioflupane SPECT may be used to differentiate dementia with Lewy bodies from other types of dementia, such as prototypical Alzheimer's disease.