Dopamine Transporter and Receptor Scintigraphy

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1. Introduction

Presynaptic as well as postsynaptic parts of the nigrostriatal dopaminergic neurotransmission can be visualized and quantified by PET and SPECT, and this information may be of value in routine practice of parkinsonian patients.
The presynaptic part of the nigrostriatal pathway can be imaged using radiopharmaceuticals that bind to the dopamine transporter, which is expressed exclusively in dopaminergic neurons, and predominantly in the cell membrane of the neuron terminals. The extent of the in-vivo binding reflects the integrity of nigrostriatal dopaminergic cells. Consequently, dopamine transporter imaging can detect degeneration of nigrostriatal cells in-vivo. Radiopharmaceuticals that bind to dopamine D2/3 receptors can help to assess the postsynaptic dopaminergic neurotransmission in the striatum, since these receptors are expressed predominantly on non-dopaminergic cells.
In the past decades, many PET as well as SPECT tracers have been successfully developed to image the dopamine transporter and dopamine D2/3 receptors. However, only the SPECT tracers ^{123}I-FP-CIT (^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane; ^{123}I-Ioflupane; DaTSCAN) and ^{123}I-IBZM (^{123}I-3-iodo-6-methoxybenzamide) are registered in the Netherlands. In the brain, the nigrostriatal pathway represents the most abundant dopaminergic projection. Parkinson's disease (PD) is characterized neuropathologically by severe loss of dopaminergic neurons. Early in the disease process of PD, particular projections of the substantia nigra to the putamen are lost. This loss may occur many years before the classical motor signs of PD emerge. In the vast majority of patients, symptoms are initially limited to one side of the body. This pattern is frequently observed on typical dopamine transporter scans in early cases of PD: the binding of ^{123}I-FP-CIT is lower in the putamen than in the caudate nucleus, and the binding may be asymmetrical. Not only PD is characterized by loss of striatal dopamine transporter binding, movement disorders such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) also display this loss. In addition, dementia with Lewy bodies (DLB) is characterized by loss of the striatal dopamine transporter. ^{123}I-IBZM SPECT can be of value in differentiating PD patients from MSA and PSP patients. While striatal dopamine D2/3 receptor expression may be preserved in early PD, loss of striatal dopamine D2/3 receptors is seen early on in MSA and PSP patients.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

^{123}I-FP-CIT: to confirm or exclude loss of nigrostriatal neurons in inconclusive cases.
For example, to differentiate PD from essential tremor, or DLB from Alzheimer's disease.

^{123}I-IBZM: to confirm or exclude loss of striatal dopamine D2/3 receptors in inconclusive cases. For example, to differentiate PD from MSA.

4. Relation to other diagnostic procedures

Loss of nigrostriatal dopaminergic cells can also be visualized and quantified using ^{18} F-DOPA PET, or radiopharmaceuticals that bind to the vesicular monoamine transporter type 2. There are some indications that dopamine transporter imaging may be more sensitive in detecting nigrostriatal degeneration than ^{18}F-DOPA PET.

In clinical studies ^{18}F-FDG PET has been shown to detect occipital hypometabolism in DLB. However, dopamine transporter imaging is more sensitive for distinguishing between DLB and Alzheimer's disease.

^{18}F-FDG PET may be more accurate than ^{123}I-IBZM in discriminating between PD and syndromes like MSA and PSP.

5. Medical information necessary for planning

- Brief medical history, including site of onset of parkinsonian and/or cognitive symptoms, and disease duration. Also location and extent of vascular brain lesions.
- List of current medication, including those recently/ temporarily stopped and date on which stopped. The patient's medication must be checked against a list of known drugs which may infer with the radiopharmaceuticals ^{123}I-FP-CIT and ^{123}I-IBZM.

6. Radiopharmaceutical

Tracer:	^{123}I-FP-CIT (^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl} nortropane; ^{123}I-Ioflupane; DaTSCAN)
	^{123}I-IBZM (^{123}I-3-iodo-6-methoxybenzamide; ^{123}I-Iolopride)
Nuclide:	Iodium-123
Activity:	185 MBq ^{123}I-FP-CIT
	185 MBq ^{123}I-IBZM
Administration:	Intravenous

7. Radiation safety

^{123}I-FP-CIT or ^{123}I-IBZM should not be administered to pregnant patients. Breast feeding must cease, since ^{123}I is secreted in breast milk. ^{123}I-FP-CIT or ^{123}I-IBZM should not be administered to pregnant patients. Breast feeding must cease, since ^{123}I is secreted in breast milk. Breast feeding should be interrupted for at least 3 weeks according to ICRP 106. The effective dose equivalent for ^{123}I-FP-CIT and ^{123}I-IBZM is 0,024 and 0,034 mSv/ MBq, respectively.

8. Patient preparation/essentials for procedure

Drugs that can interfere with the binding of ^{123}I-FP-CIT and ^{123}I-IBZM to the dopamine transporter and dopamine D2/3 receptors, respectively, should be stopped. Ideally, they should be stopped for at least 5 half-lives (see chapter radiopharmaceuticals).The decision to stop any medication must always be made by the specialist in charge of the patient's care and taking into account the pros and cons of doing so.

To prevent uptake of free radioactive iodide, it may be recommended to apply thyroid blockage (e.g., 100 mg potassium iodide) 1 h before injection of ^{123}I-FP-CIT or ^{123}I-IBZM.

9. Acquisition and processing

Brain SPECT studies should be performed on a 2- or 3-headed SPECT system, or on a brain-dedicated system. The optimal time to acquire ^{123}I-FP-CIT or ^{123}I-IBZM images is 3-6 and 1,5-2 h after the bolus injection. It is important to prevent head movements during the acquisition. The optimal energy window is 159 keV, and fan beam or LEHR collimators should be used. The pixel size should be 3 to 4 mm. The total acquisition time must be around 30 min.

10. Interpretation

In healthy controls as well as patients without nigrostriatal degeneration (and no major vascular brain lesions), the ^{123}I-FP-CIT binding is intense in both the caudate nucleus and putamen, but can be slightly asymmetrical. For routine clinical studies, binding in the cerebellum or occipital cortex may be used to assess non-specific binding. In PD patients, the binding is typically lower in the putamen than in the caudate nucleus, and is frequently asymmetrical. Binding in the putamen contralateral to the symptoms is commonly lower than the ipsilateral putamen binding. Although sometimes the ipsilateral binding is lower, or the loss is symmetrical. Also, the degeneration is commonly more severe dorsally as compared to the ventral parts of the striatum. The same scintigraphic pattern can be present in MSA or PSP patients. The rostrocaudal gradient can be flatter in the latter two forms of neurodegeneration as compared to PD. In corticobasal degeneration, patterns have been described which are typical for PD, but also normal binding as well as very asymmetrical striatal binding have been described. Recently, some studies suggested that pattern recognition can be helpful to differentiate PD from cases of vascular parkinsonism. In DLB, binding is most often much lower in the putamen than in the caudate nucleus, although sometimes the rostrocaudal gradient is rather flat. Dopamine transporter binding might also be abnormal in a subgroup of patients suffering from frontotemporal dementia. Sometimes, extrastriatal ^{123}I-FP-CIT binding can be recognized, particularly in the thalamus/hypothalamus and brain stem. The potential value of this extrastriatal binding for diagnostic purposes is not yet established.

The expression of the dopamine transporter declines by natural ageing. So, for the interpretation and quantification of dopamine transporter studies, ageing effects should be taken into account.

Since the quantification of striatal dopamine transporter binding depends on camera type, collimator, filtering, etc, it is important to always acquire and reconstruct dopamine transporter images in the same way. For quantitative purposes, data should be compared using a reference database that takes these factors into account as well as ageing effects.

In healthy controls as well as patients without nigrostriatal degeneration (and no major vascular brain lesions), the ^{123}I-IBZM binding in both the caudate nucleus and putamen is higher than in the cortical areas and the cerebellum, and it may be slightly asymmetrical. In early PD patients, the binding is slightly higher in the putamen that corresponds to the more depleted putamen. In MSA/PSP patients, the loss of IBZM binding is commonly present in both the caudate nucleus and the putamen and can be quite symmetrical.

Visual examination of the images should always be supported by a quantitative analysis, taking ageing into account, since also the expression of dopamine D2/3 receptors decline by natural ageing.

11. Report

Describe the amount of radioactivity injected, the time-point of acquisition of the images as well as the quality of the images.

Regarding ^{123}I-FP-CIT SPECT studies, it is important to describe binding in both the caudate nucleus and putamen bilaterally, and if the binding is asymmetrical. The quantification should be described. Finally, it is important to conclude whether the study supports nigrostriatal dopaminergic degeneration or not.

Regarding ^{123}I-IBZM SPECT studies, it is important to describe binding in the striatum bilaterally, and to conclude whether the study supports loss of striatal dopamine D2/3 receptor binding or not.

12. Literature

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