1. Introduction

a. The use of Fluoro-18-L-Dihydroxyphenylalanine (18F-FDOPA) in PET was developed in the 80’s for the visualisation of the dopaminergic system in patients with degenerative disorders, such as Parkinson’s Disease (PD) and related disorders. The first publication on the use of 18F-FDOPA PET for brain imaging was in 1983, which was followed by many others on the use of 18F-FDOPA PET for the diagnosis of Parkinson’s disease. Years later, in 1999, the first publication on the use of 18F-FDOPA PET for imaging of neuroendocrine tumours appeared. The value of 18F-FDOPA PET has now been proven for the diagnosis and staging of many neuroendocrine tumours, brain tumours and congenital hyperinsulinaemia of infants. The increased use of 18F-FDOPA PET has led to commercial availability of this tracer in several countries. In the Netherlands, availability is still limited to centres which have a cyclotron.

b. The 2013 Dutch guidelines for neuroendocrine tumours, suggest 18F-FDOPA PET for patients suspected of neuroendocrine tumours which are negative on somatostatin receptor scintigraphy.

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

a. Patients suspected of a presynaptic dopaminergic deficiency such as Parkinson’s Disease (PD), Multi System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and Cortico Basal Degeneration (CBD) or dementias e.g. Diffuse Lewy Body Disease (DLB).

b. The detection and staging of primary neuroendocrine tumours and their metastases.
   - Carcinoid tumours
   - Medullary thyroid carcinoma
   - Paragangliomas
   - Phaeochromocytomas

b. 18F-FDOPA PET can be of benefit for the detection of:
   - Pancreatic Isletcell tumours
   - Merkelcell tumours
   - Brain tumours

d. Congenital Hyperinsulinaemia
4. Relation to other diagnostic procedures

a. Parkinson’s Disease and related disorders

- $^{123}$I-FP-CIT SPECT can also be used to diagnose presynaptic dopaminergic deficits. $^{18}$F-F-DOPA PET scans assess striatal DOPA decarboxylase activity and storage capacity of $^{18}$F-dopamine, whereas $^{123}$I-FP-CIT SPECT binds to the dopamine transporter. In Parkinson’s Disease, MSA, PSP and CBD, the number of dopamine transporters are reduced. The sensitivity and specificity of $^{123}$I-FP-CIT SPECT is approximately equal to $^{18}$F-FDOPA PET scan. A disadvantage of $^{123}$I-FP-CIT SPECT is the longer scanning time compared to $^{18}$F-FDOPA PET, which can be a problem in this patient group.

- Post synaptic imaging is reported to be reduced in MSA but not in PD. Therefore postsynaptic imaging may possibly be used to differentiate between PD and related disorders. The postsynaptic dopaminergic system can be visualized with either SPECT or PET, e.g. $^{123}$I-IBZM SPECT or $^{11}$C-raclopride PET. However, it is difficult to differentiate between iPD, MSA, PSP and CBD, due to an overlap in binding potential of both $^{123}$I-IBZM and $^{11}$C-raclopride. Postsynaptic DOPA imaging cannot be used for differentiating between healthy individuals on the one hand and PD and related disorders on the other hand.

- By combining $^{18}$F-FDG PET and $^{18}$F-FDOPA PET, it is possible to distinguish between Parkinson’s Disease, MSA, PSP and CBD. With this combination, the sensitivity and specificity rise above 90%.

b. Neuroendocrine tumours

- For a long time, $^{111}$In-pentetreotide has played a primary role in the diagnosis and staging of neuroendocrine tumours. The $^{111}$In-pentetreotide scan can also be used to assess whether patients are suitable for PRRT.

- Recently, $^{68}$Ga labelled somatostatin analogues have become available for PET imaging. The size of the synthesis units and the accessibility of raw materials needed for this synthesis, make this tracer easily available for widespread use in PET. $^{68}$Ga labelled somatostatin analogues are a good alternative to $^{18}$F-FDOPA PET in neuroendocrine tumours.

- In patients with neuroblastoma, MIBG scintigraphy is still the method of choice. There is evidence that $^{18}$F-FDG PET, $^{18}$F-FDOPA PET and $^{18}$F-Dopamine PET are good alternatives for the diagnosis of neuroblastomas. However, $^{18}$F-FDG PET, $^{18}$F-FDOPA PET and $^{18}$F-Dopamine PET should be considered experimental for this indication.

- MIBG has long been used in the diagnostic work-up for adrenal pheochromocytomas. However, $^{18}$F-FDOPA PET seems to have a higher sensitivity for the detection of metastasized disease.

- $^{18}$F-FDOPA PET seems to have a better sensitivity for the detection of paragangliomas, as compared to $^{111}$In-pentetreotide. This has been published only in small studies. Both $^{18}$F-dopamine en $^{18}$F-FDOPA PET seem to be a good first choice for the detection of paragangliomas, but in patients with SDHB gene mutations, $^{18}$F-FDG PET is preferable.

- For neuroendocrine tumours, $^{11}$C-5-HTP can be used as an alternative. $^{11}$C-5-HTP is a precursor in the serotonin pathway, which is active in many neuroendocrine tumours. Very few publications are available on this topic, and due to the
complex synthesis, it use seems limited to pancreatic islet cell tumours.

- The use of $^{18}$F-FDG PET is limited to patients in whom dedifferentiation of neuroendocrine tumour lesions is suspected. Generally, $^{18}$F-FDG PET has a low sensitivity for the detection of neuroendocrine tumour lesions.

5. Medical information necessary for planning
- Any signs or symptoms relating to a presynaptic dopaminergic defect (PD, MSA, PSP, CBD, DLB), including use of medication, lateralisation of symptoms and duration of symptoms
- Symptoms associated with neuroendocrine tumours
- Biochemical findings, biomarkers indicative of a neuroendocrine tumour
- Possible localisation of tumour, based on previous imaging
- Use of COMT inhibitors, chemotherapy, radiotherapy or somatostatin analogs as treatment? If so, until when?

6. Radiofarmaceutical
Tracer: $^{18}$F-fluorodihydroxyphenylalanine ($^{18}$F-FDOPA)
Nuclide: Fluorine-18
Activity: Parkinsonism 200 MBq, Neuroendocrine tumours standard 200 MBq or > 1,5 MBq/kg, minimum 80 MBq
Administration: Intravenous

7. Radiation safety
- The effective dose equivalent for adults ranges from 0,025 mSv/MBq
- Clinical information is necessary to compare the benefits to the possible harm of carrying out any procedure in patients known or suspected to be pregnant
- According to ICRP 106 there is no need to interrupt breastfeeding

8. Patient preparation/essentials for procedure
- For diagnosis of PD, related disorders and DLB, patients have to stop using COMT inhibitors 5 half-lives before scanning. Other drugs used for PD can be continued.
- For the diagnosis of neuroendocrine tumours, all medication can be continued.
- For the diagnosis of congenital hyperinsuleniemia, diazoxide, octreotide and glucagon should be stopped 48 h before injection of $^{18}$F-DOPA.
- Theoretically, a higher tracer uptake could be realised by patients fasting 2-6 h nbefore this procedure. However, thus far, there is no evidence to support/disprove this theory. All studies of $^{18}$F-FDOPA PET and Parkinsonism have been performed in a fasting state, therefore, it seems fit to follow this guideline.
- Patients should not take any amino-acid containing foods 6 h prior to this procedure. Prehydration by drinking up to 1 liter of water prior to the injection of $^{18}$F-FDOPA is important to decrease the $^{18}$F-FDOPA urinary concentration.
- All patients, excluding patients suspected of pancreatic problems, should be premedicated with 2 mg/kg carbidopa 60 min prior to injection of $^{18}$F-FDOPA. Carbidopa inhibits the peripheral conversion of $^{18}$F-FDOPA to $^{18}$F-FDopamine. $^{18}$F-FDopamine is excreted actively by the kidneys, therefore, premedication with carbidopa results in increased availability of $^{18}$F-FDOPA for striatal or tumoral...
uptake. Additionally, this premedication lowers the radiation exposure of bladder and kidneys. However, in patients with congenital hyperinsulinaemia and pancreatic neuroendocrine tumours, premedication with carbidopa lowers $^{18}$F-FDOPA uptake by pathological processes in the pancreas. This can result in a false negative scan.

- In patients with extensive neuroendocrine disease and extensive liver metastases it is advised to administer $^{18}$F-FDOPA slowly in 2 min. This reduces the possibility of the development of a carcinoid crisis in these patients.

a. Schematically:
   - PD, related disorders and DLB
   - no amino-acid intake 2-6 h prior to $^{18}$F-FDOPA injection
   - 90 min prior to $^{18}$F-FDOPA injection 2 mg/kg carbidopa (max 150mg) orally, start prehydration.
   - 90 min after $^{18}$F-FDOPA injection (200MBq), start scanning.

b. Neuroendocrine tumours
   - no amino-acid intake 2-6 h prior to $^{18}$F-FDOPA injection
   - 1 h prior to $^{18}$F-FDOPA injection 2 mg/kg carbidopa (max 150mg) orally (however, no carbidopa in patients with pancreatic pathology), start prehydration.
   - 1h after $^{18}$F-FDOPA injection, start scanning.

9. Acquisition and processing
   - The patient should be placed in a comfortable position with the head fixed, using the orbitomeatal line as a reference
   - State of the art PET-CT scanner with full ring detectors LSO/LYSO/BGO/GSO crystal. Acquisitions should not start earlier than 30 min after injection and may start up to several hours after injection for detection of tumours. For imaging the brain, acquisition should start 90 min after the injection of the tracer
   - Acquisition-time 6 min (3D-mode)
   - CT-based attenuation correction with low-dose CT scan if only for attenuation purposes
   - Image reconstruction in the form of trans axial images with a matrix of at least 128x128
   - The reconstruction methods and choices of iterations, subsets and smoothness depend on the type of camera and recommendations of the manufacturer
   - Use a continuous colour scale for displaying the images
   - Absolute quantification is not possible with static FDOPA images. Only dynamic data acquisition with arterial sampling allows for absolute quantification. (These protocols are beyond the scope of this document. See European Association of Nuclear Medicine and Society of Nuclear Medicine guidelines.)
   - However for static imaging, various software programs for voxel based quantification and brain mapping with or without normal databases are available
10. Interpretation

a. Visual interpretation $^{18}$F-FDOPA PET

- Normally, after carbidopa pre-treatment, a moderately increased uptake is seen in the striata as compared to other brain regions. Also, low intensity uptake in the heart, liver, and bowels can be noted. Pancreatic uptake can be inhomogeneous due to the tissue composition of the pancreas. The uptake in the pancreatic head seems more intense as there is more tissue present in the head compared to the tail.
- Increased $^{18}$F-FDOPA uptake is seen in the kidneys, ureters and bladder.
- Lightly asymmetrical uptake can occur in the adrenal glands. However, when there is intense uptake on one side, a neuroendocrine tumour should be considered.
- Normally, no bone marrow uptake is seen on $^{18}$F-FDOPA PET scans.
- The $^{18}$F-FDOPA uptake in the gallbladder is usually intense. Gallstones may lead to inhomogeneous uptake. Correlation with CT is warranted for superficial liver lesions.
- Female patients may show low intensity uptake in the areolas. This is physiological.

b. Semiquantitative interpretation of $^{18}$F-FDOPA PET

- Thus far there is no evidence that the SUV (standard uptake value) gives any indication of response to therapy in neuroendocrine tumours.
- For brain imaging, a standard template with ROIs should be positioned around the caudate nucleus, the striatum and the occipital cortex as the reference region. The striato-occipital ratio (striatal uptake divided by non-specific brain uptake) should be calculated and compared to normal values, obtained within each department.

11. Report

a. $^{18}$F-FDOPA PET brain scans

- Scans must be interpreted visually. The uptake pattern in the striatum must be noted. This is symmetrical in the normal population. Also, compare the different areas of the striatum. Quantitative analysis of the scans is also possible by means of a standard template of ROIs. ROIs should be positioned around the caudate nucleus, the putamen and the occipital cortex as a reference region. The striato-occipital ratio (striatal uptake divided by non-specific brain uptake) should be calculated and compared to normal values, obtained within the department. This data helps to determine whether the uptake pattern fits with a presynaptic dopaminergic defect. $^{18}$F-FDOPA PET scans cannot differentiate between PD, MSA, PSP, CBD or LBD and these specific diagnoses can thus not be made based on $^{18}$F-FDOPA PET imaging solely.

b. $^{18}$F-FDOPA PET whole body scans

- Reconstructed images must be analysed from the computer monitor. Both attenuation corrected and non-corrected images should be evaluated, thereby paying attention to physiological uptake in the brain, adrenal glands, kidneys, urethra, urinary bladder, gall bladder and bile ducts. Abnormal, focal uptake of $^{18}$F-FDOPA must be described, noting both size and intensity. With regards to
the adrenal glands, special attention should be paid to symmetry of uptake. Asymmetrical uptake can point to a neuroendocrine tumour in one of the adrenal glands.

- Uptake can be quantified using SUV. However to date there is no evidence that the SUV of neuroendocrine tumours has a relation to therapy response.

12. Literature
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