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## Original Articles

# BELGIAN SOCIETY FOR NUCLEAR MEDICINE

# Guidelines for Brain Radionuclide Imaging

## Perfusion Single Photon Computed Tomography (SPECT) using Tc-99m Radiopharmaceuticals and Brain Metabolism Positron Emission Tomography (PET) using F-18 fluorodeoxyglucose

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*Purpose*

*The purpose of these guidelines is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of brain perfusion SPECT studies using Tc-99m radiopharmaceuticals and brain metabolism PET studies using F-18 fluorodeoxyglucose (FDG). These guidelines have been adapted and extended from those produced by the Society of Nuclear Medicine (Juni et al., 1998) and the European Association of Nuclear Medicine by a Belgian group of experts in the field trained in neurology and/or nuclear medicine. Some indications are not universally approved (e.g. brain death), but largely supported by the literature. They have been included in these guidelines in order to provide recommendations and a standardised protocol.*

### Background information and definitions

Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) of the brain are techniques for obtaining images of the 3-dimensional distribution of a radiopharmaceutical, which reflects regional cerebral perfusion or metabolism. SPECT is widespread and sufficient in most clinical indications. PET has a higher resolution, but at higher cost and lower availability. The latter should be used when absolute quantification is necessary and is preferred when discrete anatomical structures, especially the deep nuclei, have to be imaged.

In many neurological disorders, regional cerebral blood flow (CBF) and glucose metabolism are tightly coupled ; therefore, results of one technique may be extrapolated to the other. Flow and glucose metabolism mismatch may be however encountered in subacute stroke, acute trauma, epilepsy, and tumour.

### Clinical indications

Common indications of CFB-SPECT and FDG-PET at this time include dementia and differential diagnosis of Parkinsonian syndrome, evaluation of cerebrovascular disease, presurgical detection of seizure focus and evaluation of suspected brain trauma. Although the diagnosis of brain death is established on clinical criteria, several ancillary tests may be used for the confirmation of the diagnosis, including cerebral blood flow study (Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, 1996 ; Camargo, 2001 ; Catafau, 2001). The clinical importance of correctly assessing CBF in suspected brain death warrants its inclusion in these guidelines.

| CBF-SPECT | FDG-PET |
|---|---|
| Evaluation of patients with suspected dementia | |
| Presurgical localisation of epileptic foci | |
| Detection and evaluation of cerebrovascular disease | |
| Evaluation of suspected brain trauma | |
| Determination of brain death | |
| Differential diagnosis of Parkinsonian syndrome | |

Additional indications, including substance abuse, evaluation of suspected inflammation or infection, neurotoxic exposures and psychiatric diseases are under active evaluation. CFB-SPECT and FDG-PET methods can clearly be used to delineate functional abnormalities of the brain regardless of the cause. However, the high sensitivity of these methods in detecting functional

impairment is counterbalanced by poor specificity. Therefore, detailed knowledge of patient's symptoms and results of structural neuroimaging techniques are important for interpretation of functional images. Besides, it is only after careful study, as has occurred to date with dementia, cerebrovascular disease and epilepsy that any cause-and-effect or prognostic associations can be made (Society of Nuclear Medicine Brain Imaging Council, 1996). Tumour or neuroreceptor imaging is outside the field of these guidelines.

## Procedures

### Patient preparation

*Pre-arrival*

Patients should be instructed, if possible, to avoid caffeine, alcohol or other drugs known to affect cerebral blood flow (CBF) or glucose metabolism ($CMR_{Glc}$). Administration of psychoactive drugs, to reduce the level of vigilance or improve patient's compliance, should be avoided. If sedative drugs need to be considered, these should be administered not earlier than 5 min post-injection for Tc-99m radiopharmaceuticals and 15 minutes for FDG.

For PET-FDG imaging, patients fast for at least 6 hours to allow the establishment of a metabolic steady state, a prerequisite for glucose metabolism evaluation. Fasting advantageously diminishes FDG uptake by other organs than the brain and prevents high glucose plasma level, two causes of reduced PET-FDG image quality. Free access to water is allowed. All chronic medication should be maintained.

*Pre-Injection*

(a) The most important aspect of patient preparation is to evaluate the patient for his/her ability to cooperate. Keeping the patient informed about the whole procedure usually improves its cooperation.
(b) Achieve a consistent environment during tracer injection and uptake (it is recommended that patients in a single centre are imaged in the same conditions of motor, sensory and cognitive state) :

i. Place the patient in a quiet, dimly lit room, with ears unplugged.
ii. In most clinical situations, instruct the patient to keep his/her eyes open.
iii. Ensure that the patient is seated or reclining comfortably.
iv. Place intravenous access at least 10 min prior to injection to permit accommodation. Simultaneously for FDG-PET study, obtain a blood sample for determination of plasma glucose if there is a possibility of hyperglycaemia.
v. Instruct the patient not to speak or read.
vi. Have no interaction with the patient prior to, during or up to 5 min post-injection for Tc-99m radiopharmaceuticals and 15 min for F-18 fluorodeoxyglucose.

(c) Patients must be closely monitored at all times ; their neurologic deficits may require special care and monitoring.

### Information pertinent to perform the procedure

Relevant patient data suggested for optimal interpretation of scans includes :

- patient history, including :
  – any past drug use or trauma
  – history of epilepsy, time and type of last seizure
  – recent brain surgery or radiation therapy
- neurological examination
- psychiatrical examination, mental status examination (e.g. Folstein mini-mental examination or other neuropsychological tests)
- interictal EEG for epilepsy
- recent morphologic imaging studies (e.g. CT, MRI)
- current medication and when last taken.

### Radiopharmaceuticals

*Radiopharmaceuticals*

(a) Tc99m-Hexamethyl propylene amine oxime (Exametazime [HMPAO])
(b) Tc99m-Bicisate (Ethyl cystine dimer [ECD])
(c) 18-Fluoro-2-deoxyglucose [FDG]

*Preparation of the Radiopharmaceuticals*

(a) For Tc-99m-labelled radiopharmaceuticals, do not use pertechnetate obtained from a generator which has not been eluted for 24 hr or more. Use fresh generator eluate (< 2 hr old) for optimal results with HMPAO.
(b) Production and utilisation of FDG need to respect the Belgian Law applied to pharmaceutical drugs and, in particular, radiopharmaceuticals.

*Quality Control*

Radiochemical purity determinations of Tc-99m-labelled radiopharmaceuticals should be performed on each vial prior to injection using the method outlined in the package insert. If the percent lipophilicity is greater than 85%, the prepared product may be injected, within 30 minutes for HMPAO and 6 hours for ECD.

*Dose*

Adults 555 - 1110 MBq (15 - 30 mCi) HMPAO or ECD (typically 740 MBq [20 mCi]). Children 7.4 -

| *Mechanisms of Retention and Pharmacokinetics of Tc99m-Radiopharmaceuticals for CBF-SPECT* | | |
|---|---|---|
| Parameter | HMPAO | ECD |
| Mechanisms of Retention | Trapped in all living cells<br>Gluthatione-mediated ? | Trapped only in metabolically-intact cells<br>Deesterification |
| Peak brain activity | 2 min | 2 min |
| Brain uptake (%ID) | 2 - 3% | 4 - 7% |
| Brain washout | 12 - 15% over 15 min | 12 - 14% the first hour ; then 6%/hr |
| Excretion (% at 48 hr pi) | 50% liver-gut<br>40% kidneys | 15% liver gut<br>75% kidneys |
| Gray-matter-to-white matter ratio | 2-3 :1 | 4 :1 |

Modified from CATAFAU A. M. (2001).

11.1 MBq/kg (0.2 - 0.3 mCi/kg). Minimum dose is 110 MBq (3 mCi).

For FDG-PET, the injected dose depends on the type of acquisition and the PET system. Adults : for 3D acquisition 75 - 150 MBq [2 - 4 mCi] ; for 2D acquisition 175 - 370 MBq [5 – 10 mCi]. Children's dose (6 months - 18 years old) : scale by body surface child dose using the following formula :

$$\text{children's dose} = \frac{\text{child body surface area (normogram)} \times \text{adult dose}}{1.7\ \text{m}^2}$$

*Time interval from injection to imaging*

For HMPAO and ECD, images obtained after a 20 min delay will be interpretable. For the best image quality allow for ≥90 min delay from injection for HMPAO and 45-60 min for ECD. For both tracers, imaging should be completed within 4 hr post-injection if possible. Excessive delay should be avoided.

For FDG-PET, ≥30 min delay from injection to imaging is required for reaching a steady state.

*Radiation dosimetry*

| *Radiation Dosimetry in Adults* | | | |
|---|---|---|---|
| Radiopharmaceutical | Administered Activity (MBq) | Organ Receiving the Largest Radiation Dose (mGy/MBq) | Effective Dose (mSv/MBq) |
| HMPAO[1]<br>ECD<br>FDG[2] | 555 - 1110 i.v.<br>555 - 1110 i.v.<br>75 - 150 i.v.<br>350 - 750 i.v.* | 0.034 (kidneys)<br>0.073 (bladder wall)<br>0.17 (bladder wall) | 0.0093<br>0.011<br>0.027 |

[1]ICRP 62, page 13 and [2]ICRP 53, page 76.
* Acquisition in 3D-mode and 2D-mode, respectively.

| *Radiation Dosimetry in Children (5 year old)* | | | |
|---|---|---|---|
| Radiopharmaceutical | Administered Activity (MBq) | Organ Receiving the Largest Radiation Dose (mGy/MBq) | Effective Dose (mSv/MBq) |
| HMPAO[1]<br>ECD<br>FDG[2] | 7.4 - 11.1 i.v.<br>7.4 - 11.1 i.v.<br>Scale by body surface | 0.14 (thyroid)<br>0.083 (bladder wall)<br>0.48 (bladder wall) | 0.026<br>0.023<br>0.073 |

[1]ICRP 62, page 13 and [2]ICRP 53, page 76.
Treves S. T. *Pediatric Nuclear Medicine*. 2nd edition Springer-Verlag, 1995, p. 576.

## STANDARD IMAGE ACQUISITION

*Patient*

(a) The patient should void prior to study for maximum comfort during the study.
(b) The patient should be positioned for maximum comfort to avoid movement artifacts (blanket, pad under the knees may be used). Minor obliquities of head orientation can be corrected in most systems during processing, so that patient's comfort is more important than perfect alignment of the head. The head should be only lightly restrained to facilitate patient cooperation in minimising motion during acquisition. If cooperation is poor, sedation may be used following the injection of radiopharmaceutical. The choice of sedative agents varies widely and depends on the patient status and the local habits.

*SPECT imaging device*

(a) Multiple detector or other dedicated SPECT cameras generally produce results superior to single-detector general-purpose units. However, with meticulous care, adequate images can be produced on single-detector units by prolonging scan time to obtain $\geq 5 \times 10^6$ total counts. Longer acquisition time will yield a higher number of total counts and better quality of the final images at a higher risk of patient motion artifacts.
(b) Use of high-resolution or ultra high-resolution collimation is recommended. All purpose collimation is not suitable. Fan-beam or other focused collimators are generally preferable to parallel-hole as they provide improved resolution and higher count rates.
(c) The collimator should be positioned as close to the patient's head as possible, above the patient's shoulders and include the cerebellum in the field-of-view. Keeping the head at flexion helps to reduce the radius of rotation and to include the entire cerebellum within the field of view.

*Acquisition parameters*

(a) A 128 × 128 or greater, acquisition matrix should be used. Acquisition pixel size should be 1/3 - 1/2 the expected reconstructed resolution ; therefore, it may be necessary to use a hardware zoom to achieve an appropriate pixel size.
(b) Use 3' or better angular sampling.
(c) Although step and shoot technique is predominantly used, continuous acquisition may provide shorter total scan duration and reduced mechanical wear to the system.
(d) Total scan time is set for collecting > 5 millions counts, and therefore, depends on the imaging device. Typical scan time for a triple head camera is around 30 min.
(e) Segmentation of data acquisition into multiple sequential acquisitions may permit exclusion of bad data, e.g. removing segments of projection data with patient motion.

## Specific acquisition protocols

*Vasodilatory challenge with acetazolamide (Diamox®) or equivalent.*

(a) *Indications* : Evaluation of compromised cerebral vascular supply with or without a history of transient ischemic attack, completed stroke and/or vascular anomalies (e.g. arterial-venous malformation) and to aid in distinguishing vascular from neuronal cause of dementia.
(b) *Protocol :* acetazolamide (Diamox® [N-(5 Sulfomyl 1,3,4-thidiazol-2yl-acetamide]) is a carbonic anhydrase inhibitor that increases cerebral blood flow by inducing vasodilatation. It has been shown to increase whole brain flow 30 ± 17% in normal volunteers (Bonte *et al*., 1988). However, in hypertensive and old patients vasoreactivity may be reduced. In large vessel occlusive cerebrovascular disease, autoregulation may compensate for reduced cerebral perfusion pressure by vasodilatation of resistance vessels, masking the hemodynamic effect of large vessel stenoses. In an area of reduced perfusion reserve, where there has already been maximum vasodilatation, there is no further augmentation of rCBF following acetazolamide injection. Such areas are identified by relatively decreased tracer uptake on SPECT after acetazolamide as compared to baseline images. Comparison must be made with a baseline study performed either on a separate day or as part of a low dose/high dose technique to distinguish impaired reserve from fixed defects arising from cerebral substance loss or from baseline-only defects arising due to reduced metabolic demand. The two-day repeat study technique is simplest and may, therefore be preferable. Typically, the challenge portion is performed first. If this is normal, consideration may be given to omit the baseline study. If a baseline scan is performed, allow sufficient time for residual activity to clear (typically 24 hr). As acetazolamide is a diuretic, the patient should be instructed to void immediately before beginning of image acquisition. Acquisition and processing are identical to non-acetazolamide study.
(c) *Contraindications* :
  – in patients who have sulfonamide allergy
  – in acutely symptomatic TIA
  – during stroke in evolution (avoided within three days of acute stroke)
(d) *Dosage* : Adults 1000 mg by slow i.v. push (over 2 min). Children 14 mg/kg. The radiopharmaceutical should be injected after 20 min, when the vasodilatatory effect is most pronounced.
(e) *Adverse effects* : Light-headedness, peri-oral and distal extremity paresthesias, mild vertigo, tinnitus, short-acting diuretic-effect, and, rarely, nausea may be experienced. May induce migraine in patients with migraine history. These are generally, self-limited and do not require specific treatment. Patients may experience postural hypotension when arising and should be appropriately warned and assisted, if necessary. In the unlikely event that focal neurologic signs or symptoms develop after acetazolamide administration, intravascular volume should be restored with intravenous hydration and supplemental oxygen provided. Patients must be clinically monitored until all signs of cerebral ischemia have entirely resolved.

*Refractory epilepsy*

(a) *Ictal SPECT study* : Each patient should undergo 24-hour video-EEG monitoring with intravenous cannula at the time of the ictal SPECT study. The local neurologist/epileptologist will decide about the drug withdrawal schedule to trigger spontaneous seizures. A trained nurse or technologist should observe both the patient and the EEG. Injection of the tracer for the ictal study should be performed immediately after the onset of the seizure.
(b) *Interictal SPECT study* should also be performed in each patient. EEG monitoring prior to and during the study may be required to exclude subclinical focal seizures in epileptic patients. Patients who are suspected to be unaware of partial seizures (and are thus unable to report their frequency or occurrence), require monitoring to assure that the study is indeed interictal. At least 20 minutes before injection and 10 minutes following the injection, no epileptic activity should be detectable on the EEG. Importantly, interictal CBF-SPECT should be performed after a period of at least 24 hours without any clinical epileptic attack. Similar precautions to establish the absence of seizure activity are essential for interictal FDG-PET scan interpretation.

*Brain death*

Brain perfusion scintigraphy is a confirmatory test for the clinical diagnosis of brain death, subsequent to clinical observation and testing (Weckesser and Schober, 1999 ; Kurtek *et al*., 2000). HMPAO has been validated for this purpose using standardised protocol to avoid potential sources of errors. ECD will probably give similar results, but has not been sufficiently validated in the literature.

(a) Systolic blood pressure during injection must be above 80 mmHg in adults and 60 mmHg in children to exclude temporary cerebral hypoperfusion due to low cardiac output.
(b) Prior to patient injection, the photopeak centring should be checked.
(c) Program the computer to acquire a dynamic study of 2 seconds per frame for 45 frames (90 seconds total). Whenever possible position the gamma camera anteriorly to the head with the canthomeatal line angled 15 degrees to the collimator (the forehead will be touching the collimator, but the nose will be 3 –5 cm away from it). The field-of-view should include the neck and head.
(d) HMPAO must be injected within 30 minutes after radiochemical purity assessment. The dose is injected as proximally as possible in a bolus fashion with at least a 10 ml saline flush and start the computer acquisition simultaneously.
(e) Wait 15-30 minutes after the end of the flow study to allow brain uptake and soft tissue clearance of tracer. The presence of life support equipment may limit the availability of multiple static views to evaluate delayed tracer retention in cerebrum and cerebellum. However, the anterior and lateral views should be obtained at a minimum. Collect 300 seconds per static image. If parenchymal brain activity is visualised on the planar images, SPECT imaging is recommended if possible. In addition to the above images, single image of the injection site and of the abdomen including the liver will be obtained to check for possible technical error.

*FDG-PET*

Attenuation correction, either measured or calculated, is essential for brain studies. The method for correcting emission photon attenuation is either by :

(a) *Measured attenuation correction (transmission imaging)* : A set of corresponding images is acquired with an external source of radiation.
(b) *Calculated attenuation correction* : an estimated attenuation correction based on the emission data may be used instead of actually acquiring transmission data.

For emission images, acquisition in 3D mode is recommended following the manufacturer recommendations.

## Image processing

(a) Filter all studies in 3 dimensions (x, y and z). This can be achieved either by two-dimensionally prefiltering the projection data or by applying a 3 dimensional post-filter to the reconstructed data.
(b) Low-pass (e.g. Butterworth) filters should generally be used. Resolution recovery or spatially varying filters should be used with caution, as they may produce artifacts.
(c) When possible reconstruct the *entire* brain. Use care not to exclude the cerebellum or vertex.
(d) Reconstruct data at highest pixel resolution, i.e. one pixel thick. If slices are to be summed, this should be done only after reconstruction and oblique reorientation (if performed).
(e) For CBF-SPECT studies, attenuation correction is recommended to maintain qualitative relationship between cortical and deep structures. The Chang's method using a calculated homogenous correction matrix with an attenuation coefficient $\mu$ = 0.12-0.14 $cm^{-1}$ for Tc-99m

is commonly applied. Use shape contouring if available. Whenever possible, the surface contour should be defined individually for each transaxial slice, including scalp and not just grey matter. For FDG-PET, attenuation correction is mandatory and may be either calculated or measured with an external source or radiation.

(f) Reformat transaxial data into at least three orthogonal planes. Generate transverse sections parallel to a repeatable anatomic orientation (e.g. AC-PC line), and coronal and sagittal sections orthogonal to the transverse. Additional sections along a plane parallel to the long axis of the temporal lobes are frequently useful (e.g., for epilepsy and dementia).

(g) For FDG-PET studies, no absolute quantification of glucose metabolism is usually requested in typical clinical settings. If quantification is considered, this should be based on the autoradiographic Sokoloff's method. In a single centre, method of reconstruction should be standardised.

## Interpretation criteria

(a) Unprocessed projection images should be reviewed in cinematic display prior to viewing of tomographic sections. Projection data should be assessed for the presence and degree of patient motion, target-to-background ratio and other potential artifacts. Inspection of the projection data in sinogram form may also be useful.

(b) Images must be evaluated in the context of relevant structural information (CT/MRI). Specific attention should be paid to the extent of perfusion abnormalities relative to underlying morphologic defects (e.g. ischemic penumbra versus infarct) as well as to the possible effects of atrophy and partial-volume effect. Coregistration with anatomical images (CT/MRI) is essential when neurosurgical procedures are expected to be based on information provided by functional imaging.

(c) Images should be viewed on computer screen rather than from film or paper copy to permit interactive adjustment of contrast, background subtraction and color table. It is suggested that both pseudocolor and grey scale (monochrome) formatted images be examined. The transaxial and coronal planes of section are best utilised for interpretation, since side-to-side symmetry of CBF is the expected normal pattern. Caution must be used in selecting levels of contrast and background subtraction. Non-continuous colour scales may be confusing or misleading if abrupt colour changes occur in the range of expected grey matter activity. Thresholding, if used, must be based upon knowledge of a normal database for specific radiopharmaceuticals and instruments used in acquiring the study. Care must be exercised in choice of threshold, as artifactual defects are easily generated.

(d) The normal pattern of regional cerebral perfusion or glucose metabolism in adults resembles the distribution of grey matter due to the three to four-fold higher metabolism and perfusion of neuropil and neurones (grey matter constituents) as compared to myelinated axons (white matter). The extent of normal variability must be appreciated during scan interpretation. Substantial variability may be noted between normal individuals and between scans of a single subject obtained at different times. Individual laboratories should obtain or be familiar with a normal database to best interpret patient studies. Normal CBF-SPECT database developed by the Brain Imaging Council of the SNM is available at http://65.112.18.70/brncncl4.htm. Eyes open or closed may increase or decrease, respectively, the visual cortex activity by 30%. Other types of brain activities may influence regional cerebral blood flow. Motor and sensory stimuli have similar but asymmetric effects. Auditory stimuli effects are symmetric but less impressive. Qualitative interpretation involves comparison with the contralateral hemisphere, and/or observations of obvious diminution and tracer uptake in the brain. Scan findings should be correlated with the clinical history, recent structural imaging results (MRI or X-ray CT), and with EEG results in cases of refractory epilepsy. Digital co-registration of functional imaging data with structural imaging data (MRI, CT) is useful for interpretation if available. Three-dimensional renderings may be useful in appreciating overall patterns of disease.

(e) Semiquantitative analysis using the cortex-to-cerebellum ratio or circumferential profile may be useful in subtle changes, provided that normal fluctuations are considered. There is theoretical value of objective voxel-based statistical comparison of an individual study with a preexisting database if available. This will require additional data processing for anatomic standardisation, including AC-PC alignment, linear scaling and non-linear warping.

(f) Several specific patterns of abnormal regional glucose metabolism imaged with PET are recognised. In most instances, there are corresponding CBF patterns of abnormality, which are amenable to SPECT perfusion imaging and are summarised below according to the scan indications.

*Cognitive decline, dementia and Parkinsonian Syndrome*

Dementia is a clinical syndrome, characterised by decreased performances in cognitive domains (memory, attention, language, praxis, gnosis, and executive function), sufficient to interfere with daily life activities. Dementia is an important pathology, representing the third cause of morbidity in occidental countries (after cardiovascular diseases and cancer). Main clinical difficulties are early diagnosis and differential diagnosis. Anatomical imaging (CT scanner or magnetic resonance imaging) is mandatory to search for brain tumour, vascular lesions or other sequelae, leucoencephalopathy or hydrocephalus. Careful description of focal atrophy may also be helpful, for medial temporal atrophy is a frequent finding in Alzheimer's disease. Functional imaging is never specific enough to give a diagnosis, but it provides clinicians with important arguments for a differential diagnosis.

Several characteristic patterns of abnormal regional glucose metabolism and perfusion are recognised in the degenerative neurologic disorders and are summarised below :

(a) *Alzheimer's disease*. International diagnostic criteria (McKhann *et al*., 1984 ; APA, 1994) require a dementia syndrome with progressive evolution, in a patient with normal consciousness, without other psychiatric, systemic, metabolic or toxic aetiology. A relative reduction of CBF or glucose metabolism is seen in posterior parietal or parieto-temporal regions bilaterally. Low activity is also observed in posterior cingulate and medial parietal region. Functional impairment in frontal regions (precentral and prefrontal portions) is more variable and observed as the disease progresses. Primary cortices, basal ganglia and cerebellum are frequently preserved. The metabolic pattern in AD has been repetitively observed in numerous studies. Reduction in cerebral activity has been related to dementia severity. The pattern is less characteristic in elderly patients, where other pathologies might contribute to dementia. Measurement of activity in medial temporal region remains a matter of debate, for atrophy might greatly influence the picture. The distribution is not entirely specific for AD, and it may be observed in Parkinsonism with dementia, normal pressure hydrocephalus and dementia in patients with Down's syndrome. New programs with voxel-based analysis of brain activity allow obtaining objective assessment of abnormalities that will certainly give better opportunities for rater-independent protocols.

(b) *Mild cognitive impairment*. International diagnostic criteria (Petersen *et al*., 1997) require complaint of defective memory, progressive decline in memory that interferes only with most complex activities of daily living and normal general cognitive function that does not justify a diagnosis of dementia. The main interest is that a significant proportion of those patients will evolve to dementia in few years. Mild cognitive impairment is a syndrome, comprising heterogeneous populations, so that reliable description of metabolism will require follow up to neuropathological diagnosis. The present question is to look for activity patterns similar to AD that could give preclinical clues for subsequent dementia. However, extreme caution should accompany result description, for positive predictive value for AD is still unknown.

(c) *Frontotemporal dementia*. International diagnostic criteria (Neary *et al*., 1998) require a progressive dementia syndrome, early loss of interpersonal interaction and personal conduct, emotional blunting and loss of insight. Functional imaging shows predominant decrease of frontal activity extending sometime to the anterior portion of basal ganglia. Rather than diagnosing fronto-temporal dementia, functional imaging images a frontal syndrome. Depression is frequently accompanied by a decrease of (left) frontal activity, which is less important than in frontotemporal dementia. Slowly progressive aphasia is a rare syndrome where speech difficulty evolves in relative isolation for years. A left perisylvian decrease of activity is frequently described. Evolution to frontotemporal dementia is relatively frequent.

(d) *Vascular dementia*. They are many debates in the literature concerning vascular dementia. A first difficulty comes from the heterogeneity of vascular lesions that may cause dementia : local, strategic lesions (in thalamus), multiple brain infarcts, hypertensive encephalopathy. A second difficulty is to ascertain that there is a relationship between the vascular problem and the dementia syndrome. Dementia, vascular clinical pathology and vascular lesions on anatomical imaging are required in most diagnostic criteria. Functional imaging may demonstrate multiple sites with decreased activity distributed in vascular territories.

(e) *Extrapyramidal syndrome and possible dementia*.

1. *Diffuse Lewy Body disease*. There are several pathologies that can determine Parkinsonism and dementia. Co-occurrence of Parkinson's disease and Alzheimer's disease has been described. Diffuse Lewy Body disease is characterised at neuropathological examination by Lewy inclusions in cortical areas. Clinical criteria comprise progressive dementia, autonomic disturbances and parkinsonism (McKeith, 2000). Symptomatology fluctuations and visual

hallucinations are frequently reported. Functional imaging shows a pattern similar to that observed in AD, but reduced activity in the occipital association and primary visual cortices has been observed.

2. *Progressive supranuclear palsy* (Steele-Richardson-Olszewski syndrome). International diagnostic criteria for PSP (Litvan *et al*., 1996) comprise either vertical paresis of eye movements or early unexplained falls, accompanied by parkinsonism, pseudobulbar syndrome or frontal-type dementia (among other neurological signs). Functional imaging shows reductions in the prefrontal cortex, and to variable extent, in thalamic areas and in brainstem.
3. *Huntington's disease*. This hereditary disease is characterised by progressive evolution of abnormal choreic or athetosic movements and frontal-type dementia. Functional imaging shows bilateral reductions within the head of the caudate nucleus contrasting with preserved thalamic activity.
4. *Multiple system atrophy (MSA)* may present with mild executive dysfunction. The clinical presentation may correspond to *olivopontocerebellar atrophy (OPCA)*. Reduced glucose metabolism is seen in cerebellar hemispheres, vermis and pons, and to a variable extends in the striatum and thalamus. In *striatonigral degeneration (SND)*, activity is mainly decreased in the posterior striatum.

*Cerebrovascular diseases*

(a) Stroke

CT and MRI scans provide information mainly on anatomic changes and more recently on cerebral blood flow and volume with perfusion-weighted MRI. SPECT is a sensitive indicator of perfusion and is likely to give additional anatomic information to CT and MRI in the evaluation of cerebrovascular diseases. Abnormal patterns of blood flow are recognised either as areas of hypoactivity (focal or diffuse) or hyperactivity (hyperemia or luxury perfusion) (De Roo *et al*., 1989). Superficial hypoperfusion can be due to a cortical infarct or subcortical infarct with a mechanism of deafferentation. With both Tc99m-labelled CBF tracers, hyperperfusion is related to spontaneous recanalisation of occluded vessels. Due to the mechanisms of retention, only HMPAO is able to image luxury perfusion (defined as : "increased regional cerebral blood flow in metabolically compromised cells"). The luxury perfusion is rare within the first 9-12 hours after onset but begins to occur significantly (about 1/3 of cases) between 12 hours and 48 hours to last for several weeks (Baron *et al*., 1981 ; Ackerman *et al*., 1981). Crossed cerebellar diaschisis is frequent and is caused by disconnection of the cortico-ponto-cerebellar fibres as a consequence of stroke.

The sensitivity and specificity of SPECT for stroke localisation are 79% and 95% during the first 48 hours, respectively (Baird *et al*., 1997). The sensitivity may decrease with time because of the luxury perfusion phenomenon masking the lesion in some instances by a focal hyperaemia. The luxury perfusion may last as long as 20 days but after 30 days hypoperfusion can be again detected.

(i) Acute phase

Infarct in the anterior circulation

In the acute phase, SPECT sensitivity is dependent on time of examination and location of ischemic lesion. Sensitivity has been estimated to be 80% when SPECT is performed within 24 hours after the stroke onset (Feldmann *et al*., 1990 ; Laloux *et al*., 1994), 100% within 12 hours (Hanson *et al*., 1993), and 93% within 6 hours (Hanson *et al*., 1993). SPECT sensitivity is higher in cortical infarcts (89-95%) than in subcortical lesions (40-60%), and this might have led to an overestimation of the SPECT sensitivity in series including more patients with superficial infarcts. Crossed cerebellar diaschisis is found in about 50% of cases. As it is more frequently related to large fronto-parietal infarcts and subcortical lesions involving the internal capsule, including posterior limb, its presence may help to localise the ischemic lesion (Pantano *et al*., 1986 ; Kim *et al*., 1997).

Sensitivity of CT scan is 50%-79% within 24 hours (Wall *et al*., 1982 ; Laloux *et al*., 1994) and about 45% within 6 hours (Hacke *et al*., 1995). Several studies have shown the higher sensitivity of SPECT in comparison with CT within different time windows extending from a few hours to 48 hours (Hanson *et al*., 1993 ; Laloux *et al*., 1994 ; Dierckx *et al*., 1995 ; Baird *et al*., 1997).

MRI has become the ideal tool for early stroke diagnosis by using perfusion- (PWI-MR) and diffusion-weighted sequences (DWI-MR). On diffusion MRI, new infarcts, including also small lacunar lesions, can be seen as early as 2 hours after onset (Warach *et al*., 1995). DWI-MRI can demonstrate a new hemispheric infarct in 100% within 7 hours after stroke onset (Lansberg *et al*., 2000), 98% within 60 hours (van Everdingen *et al*., 1998), and 98% between 30 minutes and 38 hours (Ay *et al*., 1999). The accuracy of DWI-MRI to detect acute subcortical infarction is 95% (Singer *et al*., 1998). No study compared the sensitivity of SPECT with that of DWI-MR in the same patients with acute ischemic stroke. However, an indirect comparison shows that MRI has a higher sensitivity and better accuracy for anatomic localisation. DWI-MRI is also superior to discriminate new lesions from old infarcts which may make difficult the interpretation of SPECT images (Warach *et al*., 1995 ; Fisher and Albers, 1999).

In conclusion, in the acute phase (< 24 hours), SPECT is recommended for stroke localisation when MRI is unavailable, since CT scan remains normal in most cases during the first hours after stroke onset.

Infarct in the posterior circulation

SPECT does not show remote hemispheric cortical hypoperfusion in infarcts localised in the brainstem. However, it shows an occipital hypoperfusion in all patients with a posterior cerebral artery (PCA) infarct (Laloux *et al*., 1995a). In the acute phase, SPECT is only recommended in patients with clinical signs of PCA ischemia when MRI is not available. SPECT is not recommended in patients with clinical signs of brainstem infarct.

(ii) Subacute phase

In the subacute phase (> 48 hours) of cerebral hemispheric stroke, ECD should be preferred instead of HMPAO. HMPAO-SPECT is as sensitive as CT to determine the topography of stroke and therefore should not be recommended only for this purpose (Laloux *et al*., 1994). No study compared SPECT and MRI in the subacute phase, but clinical experience shows the superiority of MRI (diffusion-, FLAIR-, and T2-MRI) to localise the anatomic site of ischemic lesions. The prognostic value of ECD-SPECT is promising and should be further evaluated.

(iii) Stroke subtypes

Consideration of stroke subtype is important for treatment, recurrence, recovery, and mortality. For instance, patients with cortical infarcts are more likely to need anticoagulation than those with lacunar stroke (Brass *et al*., 1994). Even though early clinical diagnosis of stroke subtypes has been validated, there still remains some controversy over the accuracy of differentiating lacunar from nonlacunar stroke and aetiology by the neurological examination alone. Clinical examination in the acute phase predicts correct final diagnoses in 62-70% of cases only (Madden *et al*., 1995 ; Toni *et al*., 1995). Thus, the issue is raised of whether SPECT might provide additional information to CT and MRI in the early determination of stroke subtypes.

SPECT sensitivity is higher in cortical infarcts (89-95%) than in subcortical lesions (40-60%) (Feldmann *et al*., 1990 ; Laloux *et al*., 1994 ; Baird *et al*., 1997). In other terms, normal SPECT is more frequently found in association with small deep lacunar infarcts. Using this characteristic, SPECT was 68% sensitive and 100% specific for lacunar stroke. In addition, the degree of hypoperfusion is higher in cortical infarcts (mean, 27 ± 22%) than in lacunar deep lesions (mean, 9 ± 8%) (Laloux *et al*., 1994). As a result, the sensitivity and the degree of perfusion decrease may help to differentiate stroke subtypes, at least according to their respective location.

The ability to identify patients with low flow states due to asymptomatic carotid disease might permit appropriate selection of cases for endarterectomy. In symptomatic carotid occlusive disease, SPECT with acetazolamide challenge is recommended to assess the cerebrovascular reserve capacity. When the reserve capacity is exhausted, early carotid surgery or angioplasty should be performed to avoid low-flow stroke recurrence or progression in the distal field. The same rule may be applied in selected patients with severe asymptomatic carotid occlusive disease. Similarly, SPECT with acetazolamide testing may be useful in determining the potential hemodynamic risk during surgery or angioplasty. A pre-treatment impaired vascular reserve is a hemodynamic condition requiring careful monitoring of blood pressure during the procedure, the use of a shunt during carotid surgery or shorter occlusion times during the balloon inflation needed for angioplasty. SPECT with acetazolamide can also demonstrate normalisation of impaired hemodynamics after carotid angioplasty or surgery (Vorstrup *et al*., 1987).

There is no comparative study between SPECT and CT or MRI for the early (< 24 hours) assessment of stroke subtypes. However, CT scan has a poor sensitivity in the detection of early signs of infarct and therefore is not considered being useful in the determination of stroke subtypes within the first 24 hours after stroke onset (Lansberg *et al*., 2000). By contrast, DWI-MR has a particularly high sensitivity to detect early cortical and subcortical infarcts, which are related to a different mechanism, embolic or thrombotic. PWI-MR can evaluate cerebral blood volume, blood transit times, and blood flow as relative measures, and gives additional information on the hemodynamic consequences of carotid occlusion. Moreover, the occlusion site of extracranial or intracranial arteries can be seen on MR-angiography (MRA)(Fisher and Albers, 1999). Pre-MRI neurological examination alone matched final diagnoses of subtype classification in 48%, improving to 83% after DWI-MR alone, 56% after MRA alone, and 94% after DWI-MR plus MRA.

In conclusion, SPECT is recommended for early stroke subtype classification when MRI is not available. SPECT with acetazolamide testing is recommended in symptomatic carotid occlusive disease to lead to early revascularization procedure and determine the risk for hemodynamic insufficiency during surgery, when a shunt is not systematically used, and during balloon inflation for angioplasty. SPECT with acetazolamide testing may be also recommended in asymptomatic carotid occlusive disease to select the patients who are the best candidates for surgery or angioplasty.

(iv) Prediction of outcome

Age, severity of deficit, atrial fibrillation, total anterior circulation infarct stroke subtype, and some global clinical scores such as the NIH score scale, can be predictive of outcome in the acute phase, but these clinical factors have limitations for individual evaluation (Jorgensen *et al*., 1999). Moreover, they are less reliable in patients with a moderate or mild deficit. Transcranial Doppler (TCD) examination within 6 hours after stroke can help to predict both early deterioration and early improvement. If the size of infarct measured on brain CT is useful as a predictor of outcome, the relatively low sensitivity of CT in the acute stage (< 24 hours) constitutes the main drawback for an early prognostic evaluation. Several studies showed the predictive value of DWI- and PWI-MR in the acute phase, and one showed that PWI could detect hypoperfused brain tissue in good agreement with SPECT in acute stroke (Karonen *et al*., 1999). Combined MRA, PWI-, and DWI-MR can identify individual patients at risk of ischemic core progression. The presence of a mismatch between the DWI lesion and PWI hypoperfused area as well as a small DWI lesion volume is associated with a better functional outcome.

The high sensitivity of SPECT (67%) as compared with that of CT (29%) in the acute phase supports its better prognostic potential (Laloux *et al*., 1995b). A strong correlation between the degree and size of hypoperfusion and clinical outcome (functional status and/or mortality) has been demonstrated with HMPAO SPECT performed within 24 hours (Limburg *et al*., 1990 ; Hanson *et al*., 1993 ; Marchal *et al*., 2000), 12 hours (Laloux *et al*., 1995b), and 6 hours (Giubilei *et al*., 1990 ; Hirano *et al*., 2001), as well as with ECD SPECT within 12 hours (Mahagne *et al*., 2000) and 6 hours (Berrouschot *et al*., 1998b). In one study using a multivariate logistic regression model, only SPECT findings (< 6 hours) were found to be independent predictors of malignant middle cerebral artery infarction/death, offering a potential to select stroke patients for specific therapies, such as decompressive hemicraniectomy, soon after onset of symptoms (Berrouschot *et al*., 1998b). The sensitivity of ECD SPECT for fatal outcome was 82% in both visual and semiquantitative analyses, while specificity was 98% and 99%, respectively. In comparison, the sensitivity and specificity of baseline CT were 36% and 100%, respectively ; the sensitivity and specificity of clinical findings (Scandinavian Stroke Scale, depressed level of consciousness, gaze deviation) varied from 36% to 73% and from 45% to 88%, respectively (Berrouschot *et al*., 1998b). Several studies have also shown that HMPAO and ECD SPECT performed early after the stroke onset can predict the clinical benefit (Herderschee *et al*., 1991 ; Berrouschot *et al*., 1998b ; Ueda *et al*., 1999a ; Ueda *et al*., 1999b) and risk of cerebral haemorrhage before thrombolysis (Ueda *et al*., 1994 ; Berrouschot *et al*., 1998b ; Umemura *et al*., 2000). MRI (DWI-, PWI-MR, MR-angiography) can also help to select the patients who are the best candidates for thrombolysis, but no study compared both imaging techniques.

There are several ways of predicting outcome with SPECT and threshold values of SPECT indices should be appropriately chosen. Among those, patients with a lesion uptake below 40 % of the contralateral healthy hemisphere using either HMPAO or ECD have a poor prognosis, whereas higher uptake is related to better outcome (Giubilei *et al*., 1990 ; Mahagne *et al*., 2000).

In conclusion, there are many data supporting the predictive value of SPECT in the very acute stage and its usefulness in the selection of patients for thrombolysis. SPECT is thus recommended in the assessment of stroke outcome but should be ideally performed within 24 hours and within 6 hours if thrombolysis is considered. As MRI is a sensitive technique to early localise the ischemic lesion and occlusion site and to predict outcome, SPECT should be performed when MRI is not available in the acute phase.

(b) TRANSIENT ISCHEMIC ATTACK

SPECT can detect persisting hypoperfusion in transient ischemic attacks (TIAs) but its sensitivity is highly time dependent : 71% within 6 hours (Berrouschot *et al*., 1998a), 60% on the day of admission, 40% by the second day (Hartmann, 1985 ; Laloux *et al*., 1996), and much less than 40% during the first week (De Roo *et al*., 1989). Sensitivity does not seem to be dependent on the duration of TIA. HMPAO SPECT does not provide information on the cortical or subcortical location of ischemia, since its sensitivity to detect a cortical hypoperfusion is equivalent in patients with a lacunar (34%) or a superficial infarct clinical syndrome (32%). When compared with CT scan, SPECT displays a cortical hypoperfusion in 32% while CT shows a recent infarct in only 14% (Laloux *et al*., 1996). No study compared the SPECT sensitivity with that of DWI-MR in TIA patients.

The SPECT sensitivity in TIAs can be improved with the addition of reactivity testing with acetazolamide. Vasoreactivity assessment may also provide information on the mechanism of ischemia, embolic or hemodynamic, and lead to early endarterectomy in patients with carotid artery occlusive disease and unstable hemodynamic status. By contrast, without performing acetazolamide testing, the presence of persisting focal hypoperfusion was not significantly associated with some particular stroke risk and aetiological factors. The association between a hypoperfusion persisting in the days after a TIA and a recurrent infarction in

the same territory remains controversial (Laloux *et al*., 1996).

In conclusion, SPECT with acetazolamide testing is recommended in TIA patients with a carotid artery occlusive disease to detect hemodynamic insufficiency in view of an early carotid surgery.

(c) SUBARACHNOID HAEMORRHAGE

Cerebral vasospasm is a frequent complication after subarachnoid hemorrhage (SAH) and contributes to overall morbidity and mortality. Its detection plays an important role for the therapeutic strategy. Angiography is the standard test for determining the presence of vasospasm, but non invasive tests such as brain perfusion SPECT and Transcranial Doppler (TCD) can be also used for this purpose. Concordance in the detection of vasospasm between SPECT and TCD was found in 64%, but 19% of these patients however did not present vasospasm on angiography (Rajendran *et al*., 2001). SPECT can also assess the hemodynamic consequences of vasospasm with a sensitivity of 69% (Rajendran *et al*., 2001). The sensitivity of SPECT might be increased with acetazolamide testing (71% by day 18 after SAH), but there is no comparative study with SPECT without performing such testing (Kimura *et al*., 1993). The main pitfall of SPECT is that hypoperfusion can be due to other causes than vasospam, such as postoperative edema (Rosen *et al*., 1994). In order to differentiate causes of hypoperfusion, CBF-SPECT should be performed early after SAH, before vasospasm occurs. Detection of vasospasm with daily TCD should then justify a repeated CBF-SPECT for assessing patient prognosis and treatment initiated to reverse the hypoperfusion shown in the study.

In conclusion, CBF-SPECT can identify cerebral blood flow reduction due to vasospasm after SAH. CBF-SPECT and TCD are complementary methods in the detection of vasospasm after SAH and its hemodynamic consequences. Further studies should evaluate the value of SPECT when combined with TCD in the prediction of outcome.

*Refractory epilepsy*

The role of ictal-interictal CBF-SPECT and inter-ictal FDG-PET in patients with refractory seizures is the localisation of the seizure focus for surgical therapy, especially in temporal epilepsy.

Partial seizures with or without secondary generalisation are associated with focal areas of reduced CBF at or near the seizure focus during the interictal period and with dramatic increases in metabolism and perfusion in the focus and its anatomic projections during the ictal phase. Interictal imaging of glucose metabolism with PET FDG is more widely established and of greater sensitivity and specificity than interictal SPECT perfusion imaging for evaluation of refractory focal epilepsy. The detection of focal hypometabolism at the presumed site of seizure origin is highly specific (> 90%) and sensitive (> 70%) in cases of temporal lobe epilepsy. Other sites of focal origin are less frequently encountered, but may be associated with interictal hypometabolism as well. However, PET is not regularly available. In cases of temporal lobe epilepsy, the interictal zone of reduced perfusion may involve the mesial or lateral temporal structures, or both. In some cases, interictal hypoperfusion may extend outside of the temporal regions, involving large areas of adjacent frontal or parietal cortex or the ipsilateral thalamus. The additional significance of these latter patterns are not established at present. Some cases of complex-partial epilepsy are associated with epileptogenic foci in the orbitofrontal cortex, and may have associated frontal hypoperfusion.

In interpreting SPECT perfusion patterns in refractory epilepsy, it is crucial to compare ictal and interictal scans. The exact timing of tracer injection relative to observed behavioural or electrical seizure activity must be known. The scintigraphic appearance and extent of seizure foci may change dramatically depending on the exact timing of tracer injection relative to seizure onset. Areas of increase on the ictal scan, which are either normal or hypoperfused on interictal images, are related either to the focus or to its projections. The sensitivity of brain ECD-SPECT, in comparison with EEG and surgery, in temporal epilepsy is 44% and 43%, respectively, for interictal studies ; and 97% and 100%, respectively, for ictal studies.

*Mild head injury*

Although still controversial for its routine use in clinical setting, CBF-SPECT appears more sensitive than CT or MRI for revealing lesions induced by head injury, especially in the acute (<24 h) phase (Masdeu *et al*., 1995 ; Kurtek *et al*., 2000 ; Jana and Abdel-Dayem, 2001). If CT is normal and clinical examination is abnormal, CBF-SPECT shows often focal lesions (Goncalves *et al*., 1992) ; whereas, if only MRI demonstrates lesions, CBF-SPECT shows decreased perfusion presumably caused by edema (Fumeya *et al*., 1990). Therefore, the probability of finding clinical abnormalities in the absence of SPECT lesions is low, and a normal study excludes post-concussional long term sequelae with a high negative predictive value (92%) (Jacobs *et al*., 1996). As some false negative results are still possible, a normal study does not prove malingering.

Abnormalities observed on CBF-SPECT help in predicting the prognosis. However, an abnormal CBF-SPECT study is not sufficient as sole prognostic factor of the outcome ; clinical data should be considered.

*Brain death*

Normal cerebral blood flow is recognised by prompt filling of the internal carotid arteries and major vessels of the cerebrum (anterior and middle cerebral arteries). The sagittal sinus is additionally visualised in the venous phase due to normal incomplete cerebral extraction of HMPAO. Within minutes after injection, the cerebrum and cerebellum are clearly identified. Arrest of blood flow to the brain and resultant brain death is characterised by visualisation of the internal carotid circulation to the level of the base of the skull, but lack of visualisation of the cerebral circulation and brain parenchyma. The procedure represents a test to confirm the clinical suspicion of brain death. This procedure alone does not establish the diagnosis of brain death.

## Final Reporting

Each clinical report should include the following :

1) *Subject information* : name or other identifiers, age, gender, medications that may influence the results of the study.
2) *Type of study* : imaging protocol, including radiopharmaceutical, dose and intervention if performed.
3) *Indications for the study*
4) *Assessment of the technical quality of the scan* : as appropriate, mention factors that may affect the diagnostic performances of the scan (movement, deviations from usual lab protocol, hyperglycaemic state for PET-FDG study, etc.).
5) *Description of abnormalities* : the extent and severity of defects, their correlation with morphologic abnormalities and, when available, the comparison with previous examinations and reports.
6) *Interpretation and conclusions*
   A precise diagnosis should be given whenever possible. It should be based on generally accepted disease-specific patterns and in the context of known clinical history, associated co-morbid conditions, medications, and other diagnostic studies (CT, MRI, EEG). If a study cannot be interpreted based on well-accepted criteria, it should be explicitly stated in the report and considered as hypothetic. It must be recognised that many patients will present with non-specific perfusion patterns which cannot be directly attributed to a specific disorder or causative agent. Care must be taken to avoid implying the existence of cause and effect relationships between scan and behavioural/neurologic abnormalities.
   When appropriate, the full spectrum of differential diagnosis should be given. State the limitations of the offered differential diagnosis if relevant clinical data are not available, and recommend additional tests, as indicated.

## Disclaimer

The Belgian Society for Nuclear Medicine has initiated the writing and approved there guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialised practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may greatly vary from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.
Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

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