

Basic principles of Nuclear Medicine in Neurosciences

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The aim of this presentation is to draw a broad overview of the functional brain imaging in Nuclear Medicine. A more in depth description of these techniques and of their applications can be found in a recent reference (1).

All these methods have in common two fundamental steps :

- injection of radioactive substance to a patient at some time during which the status of the brain activity is known (« basal », seizure free, drug action, etc....) ;
- Tomographic imaging of the radioactive distribution after a delay that is important to monitor.

The radioactive substance is a radiopharmaceutical which has two components : a molecule of biologic interest and a radioactive atom tightly bound to it.

Thus, questions to deal with to get a better understanding of these examinations become self-evident :

What are the available radiopharmaceuticals, and which aspects of brain functions do they allow to explore ?

How can we make an image of a radioactive distribution and what are the spatial and temporal resolutions of the instruments ?

In which clinical situations do these methods give relevant and irreplaceable information ?

The radiopharmaceuticals.

1 the radioactive atoms.

They have an unstable nucleus which spontaneously emits energy to reach a stable state. This transformation is inexorable and its rate is characterized by the half-life, that is the time period during which half of the atoms of a sample have experienced it. The number of these transformations occurring in one second is the activity of the sample (unit of activity : 1 Becquerel (Bq) = 1 decay per second ; equivalence with an older unit the Curie 1 mCi = 37 MBq).

As far as we are concerned, they fall into two categories :

- the **gamma emitters** for which the transformation is associated with the emission of a photon of a precise energy.
- The **beta-plus emitters** for which the transformation is associated with the emission of a positive electron or positron of variable energy. Secondary, these positrons will slow down and collide with electrons of the medium. This event takes place after a travel of about 2 mm. depending on the initial energy of the positron (the mean of this travel distance is called the range). A dematerialisation occurs and the mass of the electron and of the positron transform in energy resulting in an emission of two photons in two opposite directions, each one with the precise energy of 511 kiloelectron-volts (keV). Figure 1.

The gamma-emitters are used to perform single photon computed emission tomography (SPECT), the main representative of this class are the technetium 99m (^{99m}Tc half-life 6 hours, energy 140 keV), and the iodine 123 (^{123}I , half-life 13 hours, energy 159 keV). In spite of its relatively short half-life ^{99m}Tc is the most easily used radionuclide, being available from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. The beta plus emitters are the core of the positron emission tomography (PET). Fluor 18 (^{18}F , half-life 110 minutes) plays a major role in PET examinations. Other atoms can be used : oxygen 15 (^{15}O half-life 2 minutes), carbon 11 (^{11}C half-life 20 minutes), 13 nitrogen (^{13}N half-life 10 minutes). They can be easily included in molecules of biological interest but their short half-lives require their on site production (cyclotron) and coupling with the other parts of the molecule.

2 the molecules of biological interest.

2.1 perfusion and energetic metabolism

Hexa-methyl-propylenamine-oxime-99mTc (HMPAO, Ceretec[®]) and Ethyl-cysteinate-dimer-99mTc (ECD, Neurolite[®]) are the radiopharmaceuticals with which SPECT perfusion brain studies are routinely performed. They are lipophilic molecules that easily go through the blood brain barrier and cellular membranes. Then they become hydrophilic in the cells (neurons and astrocytes) and thus unable to go backward across lipids layers. The involved chemical transformations are for the HMPAO a reaction with glutathione (2) and for the ECD an esterification catalyzed by a primase

specific enzyme (3). So, the radioactivity is rapidly trapped in the brain cells, proportionally in first approximation, to the local blood flow. Because of this behavior these molecules are sometimes referred to as « chemical microspheres ».

2-Fluoro-2-deoxy-D-glucose (^{18}F FDG) has been used for more than 20 years as a metabolic tracer of cells functioning. This substance diffuses through the cell membrane, this diffusion being facilitated by glucose transporters. It then undergoes a phosphorylation step by hexokinase and cannot follow further the glucose metabolic pathway. Thus the trapped activity by cells reflects their glucose consumption

^{201}Tl -chloride and $^{99\text{mTc}}$ -metoxyisobutylisnitrilme (MIBI) are radiopharmaceutical designed to study cardiac perfusion and they reflect another aspect of cell functioning. The Tl^+ ion is analogous to K^+ and is actively transported across membrane by Na^+/K^+ -ATPase. SestaMIBI (Cardiolite[®]) has an uptake dependant upon membrane electrical potential and accumulates in mitochondria.

2.2 The dopaminergic pathways.

Since the beginnings of the PET this pathway (figure 2) has received a considerable attention due to its implications in psychiatric symptoms and movements disorders (4). ^{18}F -fluoro-DOPA was used to assess the activity of dopaminergic neurons. The presynaptic components of the synapse have also been studied with ligands for dopamine transporters (DAT) which are tropane derivatives. They were at first labeled with ^{11}C as the $[^{11}\text{C}]\text{CFT}$ (5). Now, ^{123}I labeled agents are commercially available such as ^{123}I -CIT (6) and ^{123}I FP-CIT (Ioflupane, DatScan[®]) (7). Work is in progress to develop $^{99\text{mTc}}$ labeled ligands that would be more convenient for routine clinical use (8). One of them, the $^{99\text{mTc}}$ -TRODAT is already in a Phase I clinical study (9). Numerous ligands for D2 and D3 receptors have been developed, most of them belonging to the benzamides family. The ^{11}C -raclopride has been the first of them (10). More recently this kind of molecules has been labeled with ^{18}F , which is a more appropriate radionuclide for performing kinetic studies, such as fluoropropylbenzamide (11) and with ^{123}I , such as ^{123}I iodobenzamide (IBZM) (12) which opens the possibility to study D2 and D3 dopamine receptors with SPECT.

2.3 other receptors ligands

The benzodiazepine receptors

The central benzodiazepine site is a part of the gamma-aminobutyric acid (GABA) channel receptor – (GABA)_A. This site has been thoroughly studied by PET with ¹¹Cflumazenil (13,14). The equivalent SPECT radiopharmaceutical is ¹²³Iiomazenil and efforts are currently done to reach a PET-like accuracy for estimation of binding parameters of this tracer (15,16).

Many other ligands have been designed for PET imaging of the serotonin system (17-19), the cholinergic system (20). SPECT tracers are less numerous. Up to now, none of them is available for clinical routine.

2.4 Labeled amino acids

Proteins synthesis is an aspect other than the glucose metabolism by which malignant lesions may be distinguished from the benign ones. Among the different synthesized labeled amino acids the ¹¹C MethylMethionine (CMET) has had a relatively wide usage. [18F] fluoro- α -methyl-tyrosine has also been tried as a tumor marker (21). The SPECT version of this agent, ¹²³I iodo- α -methyl-tyrosine is currently under tests (22).

2.5 molecules kinetics modeling.

If the labeled molecules were completely extracted from circulation during the first pass of blood in brain tissue and irreversibly trapped there, the radioactivity distribution would be an image of the local blood flows. Even for the so-called chemical microsphere it is not exactly the case. For neuroreceptors or transporters studies, such a weighting by perfusion conditions would rather be a confounding factor, the parameter of interest being the availability of specific sites for a given ligand. Making the distinction between the **delivery** and the **binding** of a molecule and separately measuring both, are the main tasks assigned to tracer kinetic modeling (23). It is usually assumed that the labeled ligand participates to exchanges between several **compartments**, and that the tissue in which the activity is measured can be modeled as a sum of these exchanging compartments. A sequence of acquisitions is done to give the time course of activity in every voxel of interest. This evolution is compared to other ones in plasma or in some reference organ or region. Fitting to the expected evolutions derived from

the model can give access to its parameters. But it must be underlined that with a single injection it is not always possible to estimate all the parameters. For this purpose more sophisticated protocols are needed, such as coinjection of cold ligand or continuous infusion (24).

To present some definitions and techniques let us consider the one-tissue model (figure 3).

$C_p(t)$ is the plasma tracer concentration (activity) at time t (units: $\text{kBq}\cdot\text{ml}^{-1}$)

$C(t)$ is the local tracer concentration in brain tissue ($\text{kBq}\cdot\text{ml}^{-1}$)

K_1 is the rate constant for transfer from plasma to the tissue across the blood brain barrier

($\text{ml}_{(\text{plasma})}\cdot\text{min}^{-1}\cdot\text{ml}^{-1}_{(\text{brain})}$)

k_2 is the rate constant for transfer from tissue to plasma (min^{-1})

The evolutions of radioactive concentrations is ruled by the differential equation:

$$dC(t)/dt = K_1 \cdot C_p(t) - k_2 \cdot C(t) \quad (1)$$

If the system is in a steady-state $dC(t)/dt = 0$ and $K_1 \cdot C_p(t) = k_2 \cdot C(t)$

Then $C(t)/C_p(t) = K_1/k_2 = \text{cst}$.

Considering the units of K_1 and k_2 this ratio is expressed in $\text{ml}_{(\text{plasma})}\cdot\text{ml}^{-1}_{(\text{brain})}$.

It represents the volume the radioligand would occupy if it were in the brain at the same concentration as in the plasma. It defines the **volume of distribution** of the radioligand which reflects the binding potential of the brain tissue. To illustrate how these parameters can be estimated let us integrate the equation [1]

$$C(t) = K_1 \cdot \int_0^t C_p(u) du - k_2 \cdot \int_0^t C(u) du$$

Division of both sides of this equation by $C(t)$ and k_2 followed by some rearrangements yields

$$\frac{\int_0^t C(u) du}{C(t)} = \frac{K_1}{k_2} \cdot \frac{\int_0^t C_p(u) du}{C(t)} - \frac{1}{k_2}$$

This relation is the basis of Logan's graphical analysis (25). One disposes of two sets of measurements $C_p(t_i)$ (from blood sampling), $C(t_i)$ (from PET or SPECT acquisitions). Two series of values (expressed in min.)

$$\frac{\int_0^{t_i} C(u)du}{C(t_i)}, \frac{\int_0^{t_i} Cp(u)du}{C(t_i)}$$

can thus be calculated. If the model is valid, the points defined by these couples of values are aligned along a straight line, the slope of which is the distribution volume of the radioligand. Its ordinate at origin is an estimation of $1/k_2$. Usually, adjunction of a second tissue compartment (the receptor rich compartment), introducing two new rate constants k_3 and k_4 is needed to improve the fit to the experimental data.

The instrumentation

1 detection of photons.

In both modalities photons have to be detected. This is done by use of scintillating crystal, converting the energy of an incident photon in light photons. These light photons, the number of which depends on incident photon energy, are multiplied by a photomultiplier, detected and, if the energy has a suitable value, the scintillation origin is determined. The main difference between SPECT and PET is that in SPECT, a single photon does not bear information about its direction when it hits the crystal. Whereas, in PET, two photons are to be detected simultaneously (or near simultaneously) and thus it is known that the annihilation point is on the line joining the two detected points.

2 The gamma camera.

the collimator selects photons before they hit the sodium iodide (NaI) crystal. It may be designed with parallel channels or with converging channels in the transverse plane and parallels in the axial ones, resulting in a "fan-beam" geometry (26). Detector and collimator are grouped in a head that orbits around the patient. Most cameras have now 2 or 3 heads arranged for example as shown on figure 4. Only photons travelling accordingly to the direction of collimator channels are detectable. Among those ones, some are scattered and others are absorbed by the patient tissues.

3 the PET scanner.

The collimator is no longer necessary. Yet selecting devices are sometimes used to perform 2D imaging where coincidences are looked for in slices. Due to higher energy of incident photons more

dense crystals are used. Critical parameters of these crystals are their energy resolution and the duration of the scintillation after one hit, the shorter being the better in order to get a sharp time resolution to detect true coincidences. Gadolinium oxyorthosilicate (GSO) and lutetium oxyorthosilicate (LSO) are recently developed scintillators for which these parameters are well suited. The coincidences are detected inside a temporal “coincidence window” the length of which is of the order of 8 nanoseconds. Potentially, all the annihilations occurring in the object and emitting in the solid angle encompassed by the camera could be detected. But some phenomena adversely affect this sensitivity: random coincidences causing non-existent events to be detected, scatter causing to misposition true events, attenuation in the patient preventing one or two photons of the pair to reach the detector.

Nowadays, PET scanner is frequently coupled to a high quality X-rays scanner. So attenuation correction is simplified and functional and morphologic data can easily be merged.

4 imaging capabilities

What the camera yield is a set of projections of a radioactive distribution. It is the task of the reconstruction algorithm to go back to this volumic distribution (inverse problem). For years, this step was quasi exclusively based on the filtered backprojection algorithm (preceded by a rebinning (rearrangement of projections) in case of fan beam collimator or 3D acquisition). In this method a low pass filter is involved, the properties of which are important to know to achieve an adequate balance between resolution and noise. Recently, iterative methods gain a more widespread usage. They include a more realistic modeling of the acquisition process and rely on the principle of maximum-likelihood expectation maximization (MLEM). That is to say they try to compute the distribution, the acquired projection of which are the most likely the observed ones. This method is implemented for PET and SPECT with a procedure to accelerate its convergence: ordered-subset expectation maximization (OSEM) (27). For direct reconstruction of 3D PET acquisitions an analogous algorithm can be used: row action maximization likelihood (RAMLA) (28).

An important issue is the attenuation correction which can be relatively exact in PET but more problematic in SPECT where the Chang's method (29) is the most popular.

With 30 min. acquisitions the resolution (axial and transversal FWHM) is about 9 mm. for SPECT and 4-5 mm. for PET.

For an in depth review of characteristics of current PET systems see reference (30).

When the best temporal and spatial resolutions are researched one must use dedicated brain camera. This is the case for quantitative molecular kinetics studies. In the majority of the described applications this is not mandatory and the tomoscintigraphies can be performed with general purpose systems equipped with an adequate head-holder.

The clinical applications

1 cerebrovascular diseases

In this domain a lot of work was done with PET tracers not detailed in the radiopharmaceutical section as $H_2^{15}O$, $C^{15}O$, $^{15}O_2$, which allowed to study and measure perfusion (cerebral blood flow: CBF), blood volume (CBV), oxygen consumption (CMRO2) etc.... It was an extensive research field. Concerning the blood flow, many studies (31,32) reported quantitative approach to measure it in $ml.min^{-1}.100g^{-1}$ with HMPAO or ECD but no universally accepted quantification method, usable in clinical routine, emerged up to now

Let us simply recall the main results (33-35). Glucose consumption (CMRGlu) and local blood flow are coupled in most of the clinical situations (36), (there may be exception during coma, anesthesia or in post-ictal periods). Face to a decline of perfusion pressure, the first compensating mechanism is an augmentation of local blood volume. When its maximum is reached (autoregulation threshold) the CBF begins to decrease but, due to the second compensation mechanism, the augmentation of the Oxygen extraction fraction (OEF), the CMRO2 is maintained. This phase corresponds to the **misery perfusion**. Then the brain tissue enters the true ischemic zone, experiencing first a reversible dysfunction (the penumbra) then an irreversible one (37). The situation of maximum local vasodilatation was termed « oligemia » by Lassen and is a potentially dangerous one. To recognize it, in complex vascular malformation for example, a pharmacological trial with Acetazolamide

(Diamox[®]) is proposed. Oligemic regions look like normal in basal examination and like hypoperfused in the examination after Acetazolamide (38). In some circumstances the Acetazolamide reactivity may be normal in a brain territory having a low baseline perfusion. This occurs in patients with occlusive carotid artery diseases and is the sign of a blood supply adapted to a low demand. It suggests possible incomplete infarction (not visible in MRI). This hypothesis is reinforced by a diminution of benzodiazepine receptors ligands binding in these regions (39). This situation is not predictive of a subsequent ischemic stroke. When an ischemic or already damaged brain tissue is reperfused a **luxury perfusion** may occur, characterized by a reduction of OEF (40) and thus an oxygen supply in excess of demand. It is considered that this period, if associated with an increased cerebral blood flow, can be visualized by HMPAO, but not by ECD. However this hyperfixation of HMPAO is equivocal and may be due to an altered blood-brain barrier (41)

Perfusion SPECT and FDG PET had been, for a time, the only imaging modalities to unveil abnormalities and to allow a prognosis assessment at the very initial phase of stroke (42). Now this is routinely done using MRI and especially diffusion weighted imaging (43). The isotopic methods are used in a secondary period to evidence **deafferentation** and thus explain deficits which are not clearly related with the site of ischemic lesions (44). The crossed cerebellar diaschisis was the first example of such a phenomenon (45). Figure 5 shows an example of sub-cortical / cortical deafferentation.

The accumulation of these ischemic lesions, both cortical and sub-cortical, may lead to vascular dementia which is characterized by an heterogeneous aspect of the perfusion. The heterogeneity of the brain perfusion is a frequently observed aspect in normal aging (46) and one must be accustomed to examinations of this population to decide if a perfusion heterogeneity is definitely pathologic or not.

2 dementia

Of particular importance is the distinction between vascular dementia and **Alzheimer's disease** (AD). Numerous studies show that this is possible (47-49). Parietal and temporal hypoperfusion or hypometabolism, more or less symmetric is the major sign of AD. An important negative sign being the sparing of the primary cortex (visual and sensori-motor) figure 6. This pattern can be evidenced with PET or SPECT. In this domain more than anywhere else, the confrontation with clinical

presentation and morphological data is mandatory. For example, memory impairment is a prerequisite to evoke the diagnosis. Longitudinal studies are possible to assess the treatment effect (50). Moreover, functional imaging allows one to go further in differential diagnosis of dementia. A first group is the one of the **fronto-temporal lobes atrophy**, which have different clinical expressions.

The primary progressive aphasia, where language dysfunctions (syntactic and phonologic) are on the foreground. Morphologic imaging shows an atrophy of the left perisylvian region and functional examinations reveal a concordant hypoactivity (51,52).

The fronto temporal dementia. In this complex syndrome, where behavioral problems are typically the initial sign, the morphologic aspect is a frontal atrophy with an enlarged sylvian fissure. PET (53) and SPECT (54) scans show a frontotemporal decreased metabolism or perfusion. In this context, an isolated posterior hypoactivity excludes the diagnosis.

The semantic dementia is characterized by a loss of conceptual knowledges enabling to produce and understand language. This syndrome is associated with atrophy of anterior temporal lobes, usually asymmetric and more marked on the left side. This atrophy relatively spares medial regions such as hippocampus. Functional imaging shows the same pattern (55).

The posterior cortical atrophy.

Here visual functions are altered. According to the main involved region the presentation is different: visual agnosia, color agnosia or prosopagnosia when ventral pathway is concerned, alexia, agraphy, Balint's syndrome when it is the dorsal one. The functional aspect is an hypoactivity of the posterior regions associated with a relatively preserved activity on the medial temporal lobes (56).

Dementia with extra-pyramidal signs.

Some pathologies of this neurodegenerative group raise difficult differential diagnosis problems with AD. At the first rank is the **dementia with Lewy bodies (DLB)** in which fluctuation of consciousness and visual hallucinations are much more frequent than in AD. Yet, the positive diagnosis is difficult and the nosographic classification is not well established among AD variant with Lewy bodies, pure DLB (without senile plaques and neurofibrillar degeneration), Parkinson's disease with dementia. For the diagnosis of pure DLB, morphologic imaging does not appear helpful. In functional imaging, the extent of hypoactivity towards the occipital lobes looks more pronounced than in AD (57-59). **Cortico**

basal degeneration is another circumstance where functional imaging could be useful. In typical cases, the hypoactivity is asymmetric, predominant on posterior frontal and parietal lobes (60-61). The evolution is towards a more widespread involvement of the entire hemisphere including the deep structures: striatum and thalamus (61).

In these 2 latter pathologies the functional study of the dopaminergic pathway is promising. The nigrostriate function assessed by FDOPA or a tracer of the dopamine transporter is more altered in DLB than in AD.

Mild cognitive impairment

An important issue in the dementia domain is the early diagnosis of AD in a clinical situation termed “mild cognitive impairment”. More generally it can be assumed that for the involved brain cortex region hypofunction precedes atrophy. To be detected on an individual basis this hypofunction must occur in region where normal variations are limited. Although it is known that AD begins in the entorhinal cortex, an hypometabolism of this region is difficult to recognize. It appears more reliable to look for an hypometabolism in the posterior cingulate cortex (62,63)

3 movements disorders.

Parkinson’s disease (PD) is the most frequent pathology encountered in this field. But number of neurodegenerative diseases include tremor, rigidity and bradykinesia in their presentation. Since the development of ligands for dopamine membrane transporter and for D2 receptors labeled with ^{123}I or $^{99\text{m}}\text{Tc}$ the study of dopaminergic pathways is more feasible in the clinical setting (64,65). The reduction of the striatal uptake of dopamine transporters tracers is the sign of the nigrostriatal dysfunction. In PD, this reduction is predominant in the putamen and, most of the time, asymmetric (Figure 7). These results reproduce those ones of ^{18}F -DOPA PET explorations (66). Moreover, there is a correlation between the uptake reduction and the disease severity, and the time course of dopaminergic degeneration can be measured (67). In **essential tremor**, the uptake of such tracers is normal. In **multiple system atrophy** (MSA), or in **progressive supranuclear palsy** (PSP) (71) the reduction is more diffuse in the putamen and the caudate. But it does not seem possible with these

examinations to discriminate these pathologies for individual patient. Nevertheless, imaging of dopamine transporter has an impact on management of patients presenting with a possible PD or a supposed drug induced parkinsonism (study on 90 patients) (68).

Imaging of D2 receptors show a reduced striatum uptake in MSA and PSP whereas it is normal in Parkinson's disease (69).

Metabolism and perfusion studies are also used to explore these extra-pyramidal syndromes. It is noticeable that the striatal CMRGlucose is normal in PD (70). It is diminished in MSA and allows discrimination between PD and nigrostriate degeneration (72).

Current studies focus on relations between severity of the nigrostriatal dysfunction, assessed by the ^{18}F DOPA and the presence of a genetic mutation (73). Possible side-effect of long term treatment by levodopa had been explored by brain blood flow (74) showing an alteration of the response to an acute dose of levodopa in sensorimotor and ventrolateral prefrontal cortex. The neuroprotective effect of dopamine receptor agonist had been evaluated by a randomized study using the ^{123}I α -CIT (82 patients) (75).

4 epilepsy

The main issue in medically intractable epilepsy is to correctly localize the epileptogenic zone in order to determine the site and the extent of the cortical resection to be done. For this purpose several methodologies had been developed using ictal and/or inter-ictal functional studies. The general pattern is a hypometabolism in the inter-ictal phase and a hyperperfusion during the ictal period. For temporal lobe epilepsy it is now well established that inter-ictal FDG PET (76) and ictal/interictal perfusion SPECT (77) have the same efficiency in identifying the epileptogenic zone. The situation is less clear for neocortical epilepsy where subtraction from the ictal examination of the inter-ictal one, both coregistered with Magnetic Resonance Imaging (SISCOM) proved to be helpful to improve the interpretation of the SPECT data (78,79).

In all these procedures the timing of the radiopharmaceutical injection in relation to the onset of the seizure activity is of paramount importance (80,81). The localizing power of an ictal study is as much greater as the perfusion tracer is injected earlier after the seizure onset. Delayed injection results in

spread hyperactivity in which the epileptogenic zone cannot be isolated. Perfusion abnormality can last a long time after the seizure and could be related to psychotic episodes after complex partial seizure (82).

The classical pattern is sometimes missing or even inverted. Hypermetabolism during a supposed interictal phase had been thought to occur during discharge of deep epileptic focus not recorded by the surface EEG. On the contrary, hypoperfusion observed during an ictal examination could in fact unveil a « steal » phenomenon (83).

Repeated seizures can cause subtle lesions that had been evidenced by imaging the benzodiazepine receptors. A diminution of the binding potential in the cerebellum contralateral to the temporal region responsible of partial epilepsy (17 patients), mimicking some kind of « crossed cerebellar diaschisis » has been found (84).

5 tumors

Probably due to the high background activity of the normal brain, the FDG PET does not appear here so effective than in other regions. In a study including 331 patients (85) the relationship between the activity, assessed by visual inspection, and the histologic grading has been established. The FDG uptake was qualitatively measured on a four-value scale – no uptake : 0, uptake less or equal to normal white matter : 1, uptake greater than normal white matter but less than normal grey matter : 2, uptake greater than grey matter : 3. Moreover, the degree of uptake with the survival – 94% of the patients with low uptake (0,1) survived for more than one year (survival median : 28 months), whereas only 29% of those ones with high uptake (2,3) did so (survival median 11 months). Yet, it remains many clinical situations where the decision making is difficult. Differentiating tumor recurrence from necrosis or scar, especially in the case of radionecrosis and low-grade tumors, is one of them. This gave impulse for the development of more specific tracers exploring the amino acid transport across the cell membrane. ¹¹C-Methyl-Methionine has been frequently used to study brain tumors (86). With this agent, contrast of the tumor relative to the normal brain tissue is better than with the FDG. It permitted to assess the response of glioma to brachytherapy in 46 patients (87). It seems useful for differential diagnosis of low-grade gliomas (88). To overcome technical difficulties in relation with

the short half-life of the ^{11}C , other tracers, labeled with ^{18}F has been proposed as the FluoroTyrosine (89). More recently, tracers suitable for SPECT imaging have been synthesized. For example, the L-3- [^{123}I]iodo- β -methyl tyrosine (IMT) gives better results than FDG in some circumstances, such as low-grade recurrences of gliomas (90). It is also better than MIBI to distinguish progressive from non progressive low-grad astrocytomas after irradiation (91). In fact, ^{201}Tl or $^{99\text{m}}\text{Tc}$ -MIBI had been used since a very long time (92) to make a positive image of brain tumors and assess their malignancy. The physiological uptake of MIBI by choroid plexus may be confusing. A review of ^{201}Tl examinations in 90 patients with various brain tumors or processes concluded to a sensitivity of 72% and a specificity of 81 % for detecting the malignancy (93). In this study, imaging was done 15 minutes after the injection of tracer. More delayed acquisition (3 h.) is useful to further characterize the focal ^{201}Tl accumulation. The kinetic of Tl uptake can be grossly quantified by computing a tumor/non-tumor ratio in two mirror ROIs. A retention index may be defined as the ratio between the delayed and the early tumor/non-tumor ratios (94).

A strategy based upon ^{201}Tl and ^{123}I IMT has been proposed to differentiate brain tumors and was evaluated in 65 patients. (95).

Conclusion

Since a 1995 partial review of the topic (96) a lot of events have occurred:

Clinical PET has become more affordable,

Resolution of SPECT camera steadily improves,

New tracers have been designed and some of them are commercially available,

Functional MRI has gained in maturity,

Spectroscopic MRI shows endless progress but supposes extended physico-chemical knowledge.

In this continuously changing landscape, nuclear techniques still produce effective results, useful in management of dementia, medically untractable epilepsy, complex movements disorders.

The trend is to focus on more specific molecules and to more closely study their kinetics in the human brain.

Efforts are also done to better characterize what a “normal” brain distribution of a specific activity is and to quantify the pathologic deviations from it.

Thus, the concept of **molecular imaging** is emerging, which aims at detecting the pathologic processes before they cause structural modifications, in a period where they are, hopefully, more amenable to treatments.

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