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Title:

Clinical and technical considerations for implementing PET brain imaging for dementia

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PET brain imaging for dementia

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Abstract

The number of cases of dementia has dramatically increased over the last decade. Imaging the brain with PET has been used for many years, but in the past decade the radiopharmaceuticals and technology available for imaging dementia has vastly improved. In recent years, the United States Food and Drug Administration (FDA) has approved three PET radiopharmaceuticals for detecting amyloid in brain and Tau PET radiopharmaceuticals are being investigated for the use of dementia imaging in clinical trials. This paper will discuss different forms of dementia that can be imaged with PET, review common radiopharmaceuticals used for imaging dementia, and provide technical recommendations for performing the studies.

Key words: Brain, PET, Amyloid, TAU

INTRODUCTION

Positron Emission Tomography (PET) has been in use for many years to evaluate patients with a host of different types of disease including oncologic, cardiac, and neurologic etiologies (*1*). In recent years, PET has vastly improved through technological developments as well as due to an increase in the number of PET radiopharmaceuticals available for imaging. Further, by combining PET with computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI), our ability to examine cell metabolism or target specific proteins in the context of a known anatomic location has become a reality. Although computed tomography is not required for PET brain imaging, PET/CT is the preferred method for scanning brains. For years, the most widely used radiopharmaceuticals for brain imaging was 18F-fluoro-2-deoxy-D-glucose (18F-FDG) (*1*). 18F-FDG is still commonly used in clinical practice to determine cerebral glucose metabolism, and the spatial pattern of 18F-FDG metabolism is valuable in differentiating types of dementias. Alzheimers disease (AD) is a common form of dementia and is characterized by the accumulation of beta-amyloid (Aβ) protein or *senile plaque formation* and neurofibrillary tangles of hyperphosphorylated tau protein (*2*). Today several radiopharmaceuticals targeting amyloid protein are available, and specific radiopharmaceuticals targeting tau protein are in development. In this paper we discuss more readily available PET radiopharmaceuticals for imaging dementia, the guidelines for their administration, and scanning techniques.

LEARNING OBJECTIVES

Readers will be able to:

1. Discuss PET radiopharmaceuticals available for clinical imaging of dementia

2. Review the administration and scanning techniques for these radiopharmaceuticals

TYPES OF BRAIN IMAGING

In recent years several PET radiopharmaceuticals have been developed for imaging subjects with mild cognitive impairment (MCI) and dementia. Broadly, the goal of this imaging falls into three categories, detection of: 1. cerebral glucose metabolism, 2. cerebral amyloid protein, and 3. cerebral tau protein. Often preceded by MCI, dementia is defined as a group of neurodegenerative disorders characterized by memory impairment and cognitive decline, resulting in difficulty of performing the activities of daily living, that has been present for a minimum period of 6 months" (*2*,*3*). There are several different types of dementia, typically categorized according to the results of a physical examination and neurocognitive tests with imaging used to support the diagnosis. The most common types of dementia encountered in the nuclear medicine clinic are: Alzheimer's disease (AD), Lewy body dementia, frontotemporal dementia, and vascular dementia (*2*). AD is thought to account for up to 60%-80% of all dementia cases (*2*,*4*).

Cerebral Glucose Metabolism

The brain metabolizes glucose, and 18F-FDG is a glucose analogue. The cerebral metabolic rate is an indicator of normal versus declining brain function. In patients with cognitive impairment, detection of decreased cerebral metabolic rate can be valuable and a 18F-FDG scan may allow members of the health care team to follow and manage patients as they progress from MCI to dementia (*2*). 18F-FDG scan plays an important role in all brain imaging applications, and also serves as a valuable marker to differentiate AD from other causes of

dementia such as frontotemporal dementia; as an 18F-FDG scan can indicate the brain regions with decreased cerebral metabolic rate (figure1) (*5*).

Amyloid Protein Imaging

It has been suggested that the deposition of amyloid protein in the brain (Aβ accumulation) is a slow process and may extend for decades before clinical symptoms are detected (*4*). Currently, investigational drugs to treat AD are mainly focused on arresting the progression of amyloid protein deposition, which is why it is so important to have a way to image Aβ accumulation over time. Over the last few decades, several radiopharmaceuticals have been developed with the ability to detect amyloid in the brain. The first to be developed was C-11Pittsburgh Compound B (PiB). The biggest limitation for this radiopharmaceuticals was the short half-life of C-11 (20 minutes) and the need for an onsite cyclotron (*6*). More recently, three radiopharmaceuticals that use F-18 as the radioactive label have been developed (half-life of 110 minutes) and have received FDA approval. The first to receive FDA approval was 18F-florbetapir (Amyvid), next was 18F-flutemetamol (Vizamyl), and finally 18F- florbetaben (Neuraceq). It is important to remember with these imaging studies, that just because radiopharmaceutical uptake may be observed in the brain, this does not mean the patient has AD. However, a negative amyloid scan suggests that the likelihood the cognitive impairment is caused by AD is low (figure1) (*2*). With any PET radioligand, off-target uptake may be observed, and thus requires expert interpretation by a physician adequately trained in the interpretation of images from these specific compounds.

Tau Protein Imaging

The presence of neurofibrillary tangles of hyperphosphorylated tau proteins are also a hallmark for the AD (*4*). In the healthy brain, tau proteins should bind to microtubules inside neurons to help support those cells and their functions, however, in AD, changes to the chemistry of the brain can result in tau protein aggregation rather than binding to the microtubules. Over time, these form neurofibrillary tangles that disrupt communication between neurons (*7*). More recent work suggests these "tau tangles" may disrupt communication between the nucleus and body of neurons in the brain that adds to possible communication disruption mechanisms and further exacerbates neurodegeneration (*8*). Imaging with tau PET agents has shown a correlation between the severity of dementia experienced by the patient and tau pathology (*9*).

Both amyloid and tau imaging agents have corroborated well with the Braak and Braak stages of amyloid protein and tau protein deposition of AD starting from the medial temporal regions in the early stages of the disease and more widespread neocortical accumulation in the later stages (*10*). Currently, there are a number of tau PET radiopharmaceuticals being studied in clinical trials; however, none of these have been approved by the FDA or are used routinely in clinical practice.

BRAIN IMAGING GUIDELINES

Patient Preparation

Patient preparation prior to a brain PET for clinically suspected dementia should start with a detailed conversation that includes the patient and family members. Issues that need to be

discussed include: patient history, symptoms, patient/physician concerns, and instructions on how the scanning will be performed. Through this discussion, the technologist will be able to assess the brain function of the patient and will have an idea of how well the patient can cooperate during imaging. This also gives family members a chance to express their concerns and raise questions. Depending on the type of imaging ordered, specific guidelines may need to be followed for patient preparation.

For an 18F-FDG brain PET/CT scan, the patient's environment prior to scanning is very important. The patient needs to be placed in a quiet room with low ambient light and little stimuli for at least 30 minutes prior to radiopharmaceutical injection and throughout the 30-60 minute uptake time. An intravenous (IV) line needs to be placed at least 10 minutes prior to the radiopharmaceutical injection and a blood glucose test should be performed (ie. a blood glucose under 200mg/dL is recommended prior to injecting the radiopharmaceutical). The patient must have had nothing to eat or drink for at least 4 hours prior to the study (although water is allowed and daily medication may be taken with water) (*11*).

When a brain PET/CT is done using amyloid radiopharmaceuticals, there is little patient preparation needed. An IV line should be established and the patient placed in a comfortable setting. Environmental stimulation is not a concern and patients may move freely in the uptake room as desired, they may also read or watch TV. There are no food restrictions and all daily medication may be taken.

Injection of Radiopharmaceuticals & Uptake Time Guidelines

After an IV is in place, the shortest IV extension line available should be used when injecting the radiopharmaceuticals. Before radiopharmaceutical injection, inspect the

radiopharmaceutical for any particulate matter and if particulate matter is present, do not inject. All radiopharmaceuticals should be injected as a slow bolus (within 40sec) followed by a 10-20 mL saline flush of the IV line. Of note, unlike 18F-FDG, radiopharmaceuticals targeting amyloid do not allow for volume adjustment or flushing of the radiopharmaceutical syringe with saline. For details on the activity of radiopharmaceutical to administer and the uptake time please refer to TABLE 1. Once the injection is complete, the IV line can be removed.

Patient Positioning

At the end of the uptake time, the patient is asked to void. Keep in mind the mental status of the patient and make sure to allow plenty of time to use the restroom, to position the patient on the scanner, and to start the PET image at the appropriate time for optimum work flow in the PET center.

Proper head positioning for brain imaging is truly important. Before placing the patient on the table, make sure to remove all items from their pockets, jewelry from the neck up, and hearing aids. Install the appropriate radiolucent head holder. Mild rotation or movement of the head can interfere with image interpretation. Place the patient on the table in a supine position with their arms cross over their chest. The vertex of the head should reach the most superior point of the head holder. Use a foam wedge under the knees for lower back support, an arm strap to help stabilize the arms, and any other accessories needed to make the patient as comfortable as possible. Taking the time to complete the above steps is essential to reduce body movement during the scan.

Using the laser lights on the PET/CT scanner, carefully position the head such that there is no rotation. The cantho-meatal line should be oriented in the vertical position. Once the head is

in the desired position, use rolled washcloths or foam wedges to fill any gaps between the patient's head and head holder. Secure a head strap across the forehead and recheck the positioning with the laser lights (figure 2). The whole brain and cerebellum needs to be positioned in the field of view (FOV). Finally, check the vertical placement of the table to ensure the brain is centrally located in the FOV. Clearly give the patient detailed instruction of what to expect and the importance of holding as still as possible.

Imaging

Depending on the imaging equipment available and the clinical indication, a single FOV static image or a multiple sequential images of the same FOV, known as dynamic imaging, will be performed. Static imaging is useful when the standard uptake value (SUV) is of interest. To calculate SUV, the technologist must document the patient's accurate weight, height, and the actual amount of radiopharmaceutical that was injected into the patient. Dynamic imaging is useful when quantification of the regional metabolic rate is of interest (*11*). When dynamic imaging is available, it is the preferred method; however, it is generally used in research settings as the scan can take up to 180 minutes with imaging starting at the time of injection. PET brain images typically are reconstructed at a 128 x 128 or 256 x 256 matrix. Iterative reconstruction is routinely used. Other reconstruction settings can be set according to institutional and camera manufacturing guidelines. Refer to TABLE 2 for scan duration times for each radiopharmaceutical. Of note, often multiple acquisitions are acquired during the course of the scan. For example, typically 2 static images that are 5 minutes each of the brain are acquired for each 18F-florbetapir scan.

CONCLUSION

Although the underlying cause of dementia remains an enigma and a cure is still beyond our grasp, there has been a large amount of research and over the last decade to improve our knowledge about the disease, how it is diagnosed, and treated. PET of the brain is a helpful tool for confirming the diagnosis and assessing disease progression over time. In recent years, several new radiopharmaceuticals have become available for dementia imaging. With these new radiopharmaceuticals come new guidelines and recommendations to follow to obtain the best possible results for our patients.

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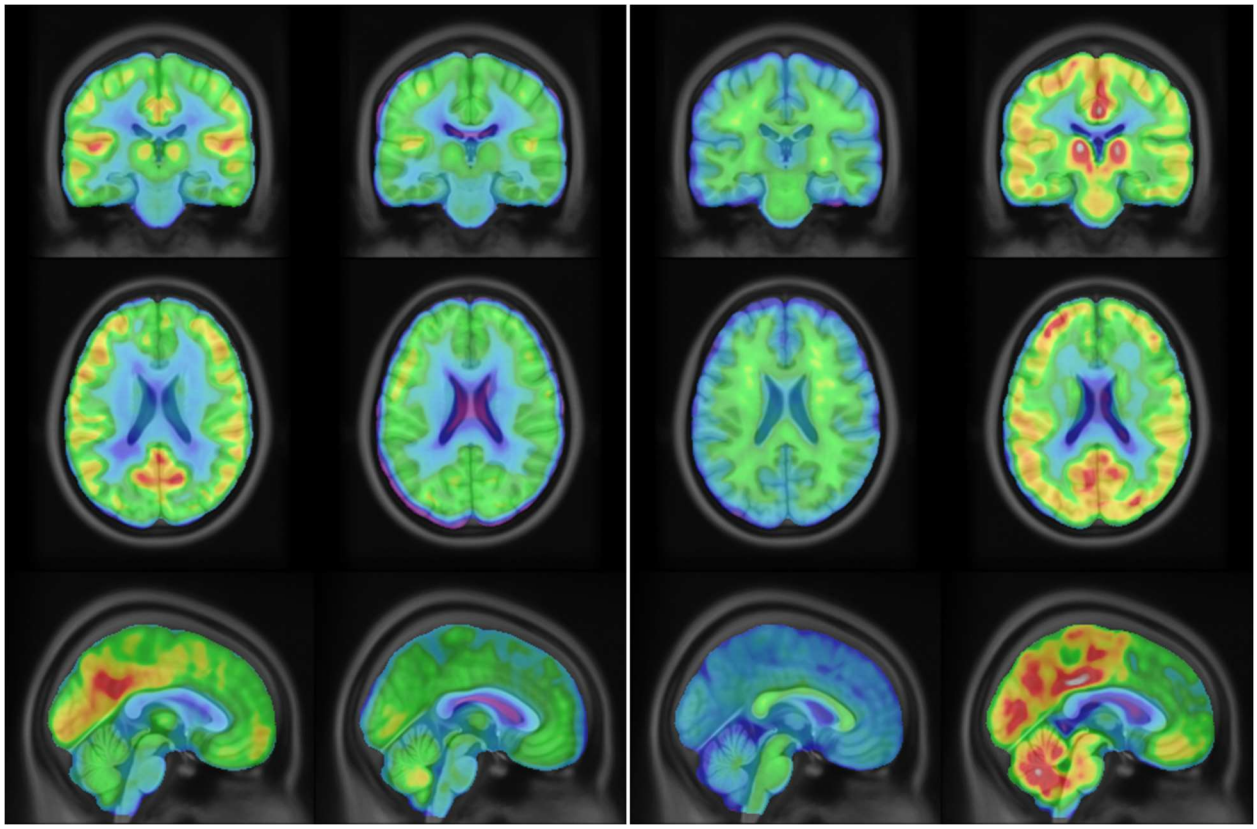

FIGURE1: Column 1 is a normal 18F-FDG scan. Column 2 is an abnormal 18F-FDG scan. Column 3 is a normal amyloid scan using Florbetapir. Column 4 is an abnormal amyloid scan using Florbetapir.

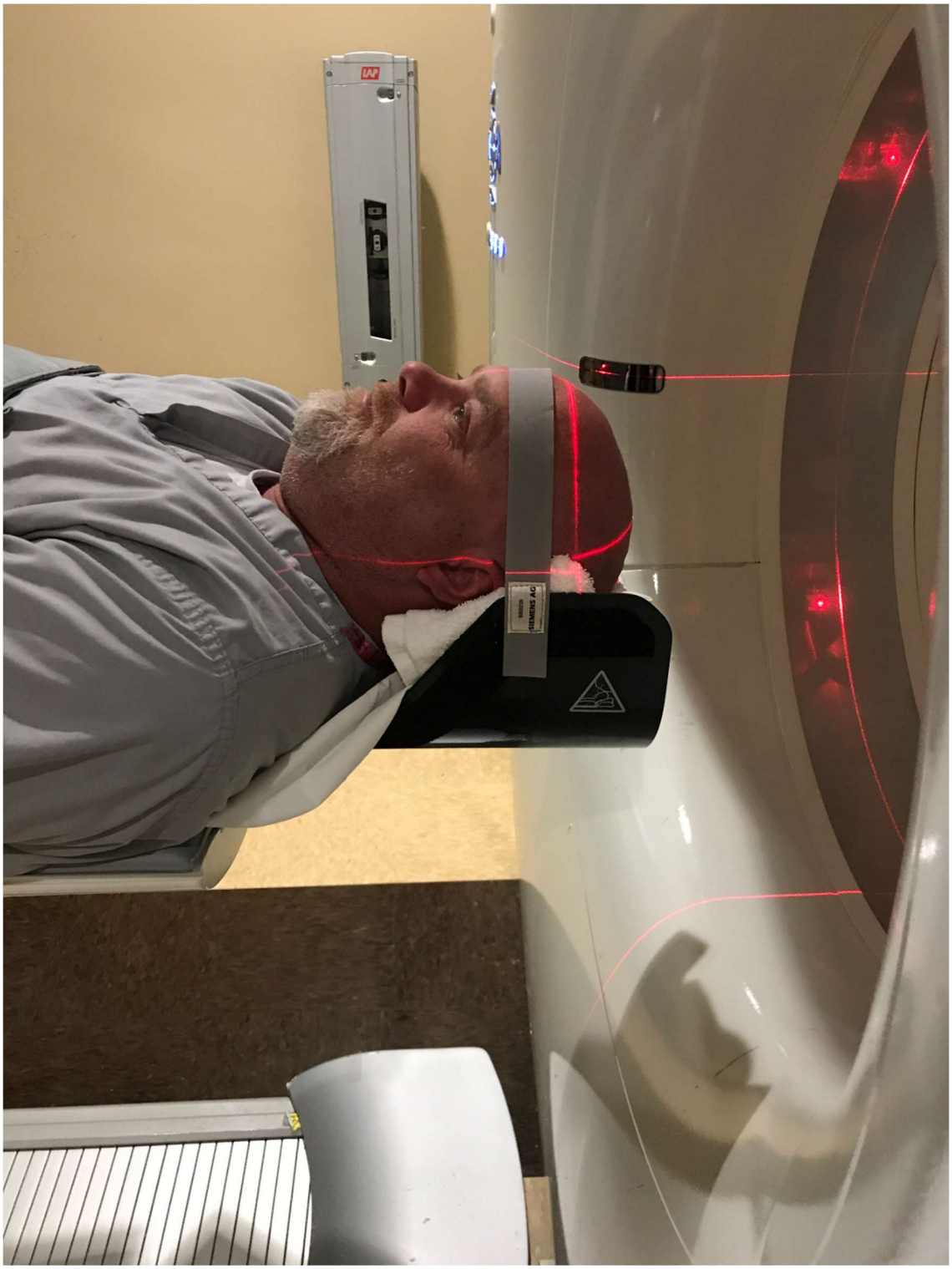

FIGURE 2: Proper head positioning shown using a radiolucent head holder with the appropriate stabilizing accessories.

TABLE 1

Tracers	**Activity Administered +/- 10% (MBq)**	**Uptake Time (minutes)**
18F-fluoro-2-deoxy-D-glucose (18F-FDG)	370	30-60
18F-florbetapir (Amyvid)	370	30-50
18F-flutemetamol (Vizamyl)	185	60-120
18F-florbetaben (Neuraceq)	299.7	45-130

TABLE 2

Tracers	**Static Image (minutes)**	**Static Sequence Imaging (frames X minutes)**
18F-fluoro-2-deoxy-D-glucose (18F-FDG)	15	3 x 5
18F-florbetapir (Amyvid)	10	2 X 5
18F-flutemetamol (Vizamyl)	10-20	2 X 5
18F-florbetaben (Neuraceq)	15-20	4 X 5