Current Status of F-18 FDG PET brain imaging in patients with dementia

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ABSTRACT

Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET) brain imaging is commonly used in the early detection and differential diagnosis of various subtypes of dementias. F-18 FDG PET images are mainly evaluated visually and semi-quantitative (SQ) analysis programs are also commonly used in many centers. However, visual and SQ analysis carry certain limitations. Visual assessment is subjective and dependent on expertise. Commercially available SQ analysis programs have certain limitations such as suboptimal selection of brain areas or erroneous uptake normalization procedure which may provide inaccurate results and physicians reporting SQ results should be aware of these. In this pictorial review article, we will discuss the current status of F-18 FDG PET brain imaging in patients with dementia and present figures and SQ analysis results of various subtypes of dementias as well as certain artifacts seen on F-18 FDG PET brain imaging studies.

Key words: F-18 FDG PET, brain, dementia, semiquantitative analysis, visual analysis
INTRODUCTION

Dementia is characterized by both memory loss and at least one other type of cognitive impairment which is decline in cognitive abilities in memory and thinking skills. There are various subtypes of dementias and management, disease course, and outcomes are different in each of them. Alzheimer’s disease (AD) is the most common cause of dementia which is usually seen after age 65. AD is characterized by accumulation of the β-amyloid peptide (amyloid plaques) and neurofibrillary tangles of hyperphosphorylated tau protein within the brain. Mild cognitive impairment (MCI) is an intermediate stage between normal age-related cognitive decline and dementia. Frontotemporal dementias (FTD) arise from degeneration of the frontal and temporal lobes which are usually seen in patients younger than 65 years. In FTD, personality change and inappropriate social conduct, with early loss of insight and blunted emotional responses, are prominent features. Dementia syndromes associated with parkinsonism include diffuse lewy body dementia (DLBD), parkinson’s disease dementia, and parkinson plus syndromes with dementia (progressive supranuclear palsy and cortical basal ganglionic degeneration). Visual hallucinations and parkinsonism (bradykinesia in combination with rest tremor, rigidity, or both) are commonly seen in patients with DLBD.

Early diagnosis of dementias allows early and appropriate use of specific medications for symptomatic treatment. Basic approach for evaluating patients with cognitive dysfunction includes detailed history, physical and neurological examination, cognitive testing, laboratory testing, specialty consultation, routine brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) to identify structural, demyelinating, inflammatory or vascular etiologies (1). Single photon emission computed tomography (SPECT) and positron emission
tomography (PET) imaging studies are used in selected difficult cases to improve diagnostic accuracy.

There are various SPECT and PET studies for dementia. The commonly performed studies in routine clinical practice are Tc-99m labeled brain perfusion radiotracers for SPECT imaging and Fluorine-18 fluorodeoxyglucose (F-18 FDG) and F-18 labeled β-amyloid imaging radiotracers for PET imaging (2). Dopamine transporter (DAT) scan/SPECT is also available to confirm dementias with parkinsonism (3). Oxygen-15 (O-15) water brain perfusion and O-15 PET imaging studies are available only in limited centers (4). Recently, tau PET ligands have been developed (5).

**F-18 FDG PET BRAIN IMAGING IN DEMENTIA**

F-18 FDG PET/CT scan is commonly used in the early and differential diagnosis of subtypes of dementias (6,7). Subtypes of dementias usually shows characteristic findings on F-18 FDG PET images (8-13). In AD, hypometabolism involves bilateral or unilateral parietal (lateral and medial/precuneus) and temporal lobes and posterior cingulate cortices (Figure 1). Hypometabolism may also involve the frontal lobes. There is usually preserved metabolism in sensorimotor cortices, basal ganglia, occipital lobes and cerebellum. In DLBD, hypometabolism involves bilateral or unilateral occipital (mainly primary visual cortex) lobes (Figure 2). Hypometabolism may also involve parietal and temporal lobes. There is preserved metabolism in posterior cingulate cortex (cingulate island sign) (13). In FTD, hypometabolism is seen in bilateral or unilateral frontal (mainly medial and anterior, also lateral) and temporal (anterior) lobes which may also involve parietal lobes and subcortical structures. In multi-infarct dementia, focal areas of hypometabolism corresponding to area of infarctions in cerebral cortical and subcortical structures and cerebellum. Diffusely reduced uptake in the hemi cerebellum contralateral to large area of
infarct (crossed cerebellar diaschisis) may also be seen. In MCI, hypometabolism is mainly in posterior cingulate cortex and hippocampus (area medial to temporal lobe).

Expert ‘visual reading’ of the F-18 FDG PET images resulted in 90% concordance with the clinical diagnosis in all subjects, specifically, this concordance was 93.4% for AD, 88.8% for FTD, and 66.6% for DLBD (7). A meta-analysis of 24 studies showed that F-18 FDG PET scan has 88% sensitivity and 84% specificity in the prediction of conversion to AD in patients with MCI (14).

F-18 FDG PET brain images are assessed visually and SQ analysis programs are also available in many centers. Visual analysis is subjective and dependent on expertise (15). Accurate visual analysis requires a good knowledge of normal distribution of F-18 FDG in various ages, characteristic distribution of metabolic abnormalities in various subtypes of dementias, and normal brain anatomy and recognizing abnormal findings on low-dose CT scan and certain artifacts on PET/CT images. In addition to assessing metabolic activity in basic brain lobes and subcortical structures, it is also important to define the metabolic activity in different parts of a lobe and in other specific areas of the brain such as anterior and posterior cingulate cortices, precuneus, hippocampus and primary visual cortex, which is important for differential diagnosis of dementias. F-18 FDG brain PET images should be reviewed in both color and gray scale. Reviewing images in color display better shows hypometabolic regions as compared to gray scale. MIP image may help better locating abnormalities in cerebral cortex in a 3D presentation (Figure 1). Various SQ analysis programs have been developed over the years to detect mild abnormalities which are not apparent on visual inspection (15-21). Herholz et al. reported that automated analysis of F-18 FDG PET provided 93% sensitivity and specificity for detection of mild to moderate probable AD and 84% sensitivity and 93% specificity for detection of very mild probable AD.
Lehman et al. reported that the diagnostic accuracy, specificity, and confidence of F-18 FDG PET interpretation improved with SQ analysis for evaluation of MCI or AD (17). However, in routine assessment of FDG brain PET studies, SQ analysis softwares carry certain limitations which we wanted to address in this article.

There are various commercially available SQ analysis programs, some are voxel-based and some ROI-based. Some programs automatically select the brain areas using brain templates/atlases and in some programs brain areas are selected manually. These programs determine if there is statistically significant difference between patient and normal values or between right and left side of the brain (asymmetry index). In the automatic selection of brain areas, global spatial normalization is used to match global spatial features of patient’s brain (position, orientation and dimensions) with a standard or brain atlas using various algorithms (22). Most commonly used brain template is Talairach atlas (Co-Planar Stereotaxic Atlas of the Brain) (23). Brain has 52 brodmann areas in each hemisphere and each area has a unique function. A recent study using multi-modal magnetic resonance images delineated 180 areas per hemisphere bounded by sharp changes in cortical architecture, function, connectivity, and/or topography (24). These regions are in various sizes and some are very small. Assessing metabolism in very small brain regions is difficult due to low camera resolution and high physiological brain activity. Registering patient’s image with a brain template/atlas and automatic selection of areas via SQ analysis programs is usually suboptimal due to complex brain anatomy (differences in the gyral and sulcal pattern), various size and shape of the brains as well as position of the head during image acquisition. Manual selection of areas without help of patient’s co-registered MRI or CT images is also not easy. Suboptimal selection of brain areas causes inaccurate SQ results particularly in small regions such as basal ganglia, and regions in close proximity such as cingulate cortex, and when assessing
uptake in a whole or part of a lobe, and specific areas such as broca’s area (Figures 1, and 2). Figure 3 demonstrate suboptimal registration with SQ analysis programs.

There is a need of developing new SQ analysis programs to better locate brain areas and more accurately assess regional changes in glucose metabolism or perfusion. PET/magnetic resonance imaging (MRI) fusion images, either via image co-registration or dedicated PET/MR camera can more accurately localize brain areas. A recent study demonstrated that PET quantitation accuracy using the MRI based attenuation correction in a dedicated PET/MRI camera is reliable in a clinical setting, and is similar to that obtained using PET/CT camera (25). Manual selection of brain areas on PET with the help of patient’s MRI can provide more accurate SQ results than automated selection of areas. This also requires knowledge of interpreting normal MR anatomy or assessing images with the help of an MR specialist. Perhaps developing a software program to open up brain gyri into a large flat area/map and parceling it to specific brain areas may help better locating areas in the brain (Figure 4). It is also important to compare brain PET images with age matched controls. In some SQ analysis programs, control ages range is suboptimal which is wide and also includes young people. Also the number of healthy control individuals in these SQ analysis programs, which is usually around 30-50, should be higher to provide more accurate normal values for comparison with the patients. Normal values may also show differences in female and male genders as well as in races.

In SQ analysis programs, normalization of brain F-18 FDG uptake is also used in which images are normalized to whole-brain activity or a reference region such as cerebellum. In patients with significant reductions in metabolic activity in whole brain or in reference region, uptake normalization procedure can generate erroneous results.
Standardized uptake value (SUV) can also be used to compare metabolic activity of brain regions (26, 27). Yamaji et al. reported that patients with moderate AD had significantly decreased cerebral metabolic rate of glucose (CMRglc) in the temporal, frontal, occipital, parietal, and sensorimotor cortices and significantly decreased SUV in the temporal, frontal, occipital, and parietal cortices (26). However, compared with the healthy persons, the patients with mild AD showed significantly decreased CMRglc in the temporal, frontal, and parietal cortices, but there was no significantly decreased SUV in any region in the same study. Ohyama et al. suggested that SUV threshold value of 5 in the parietal lobe in F-18 FDG PET study could discriminate the patients with AD from the normal subjects with a sensitivity of 86% and specificity of 90% (27). SUV is affected by many factors which could be technical errors or biological or physical factors such as extravasation of radiotracer, blood glucose level, scan acquisition parameters and many other factors (28).

For accurate results, PET images should be obtained in optimal conditions, with appropriate patient preparation, adequate radiotracer dose with injection and imaging techniques (29). Blood sugar level should be below 150 mg/dl at the time of F-18 FDG injection. When hyperglycemia is present, high circulating insulin levels drive F-18 FDG into muscle and results in globally reduced uptake in the brain in cortical and subcortical structures. Scalp/brain uptake ratio may help to determine if globally reduced uptake in the brain is due technical or non-cerebral reasons (injection of small dose of activity, extravasation of activity or presence of large markedly hypermetabolic lesions in the other parts of the body taking up majority of the activity) which causes reduced uptake in both scalp and brain versus cerebral pathologies such as brain atrophy due to normal aging which causes reduced uptake in most of the cerebral structures but not in scalp.
Physicians interpreting the images should be aware of certain artifacts (Figure 5). Major artifacts are easy to recognize but mild motion causing slight right-left shift should not be mistaken as unilateral decreased activity. PET/CT fusion images better show motion artifacts by demonstrating misregistration between the PET and CT images. Patient motion during PET acquisition or between PET and CT imaging will create artifacts on attenuation corrected (AC) PET images. Reviewing non-AC images may help in patients when repeat imaging is not possible. Non-AC PET image can grossly assess the cerebral metabolic activity (Figure 6). If the motion was during PET acquisition, a repeat image should be obtained.

Reviewing low dose CT scan of PET/CT studies may help identifying infarcts, masses or cystic lesions, which can also cause reduced F-18 FDG uptake. Radiological correlation with diagnostic CT or MRI images of the brain helps more accurately interpreting F-18 FDG findings.

Absolute quantification of CMRglc is also possible which requires dynamic F-18 FDG PET imaging and obtaining arterial blood sampling at multiple time points (30). However, this technique is time-consuming and require help of expert physicists and is not practical for routine clinical studies. F-18 FDG uptake as percentage of injected dose per gram or ml of brain can also be calculated using a formula (31).

Although each subtype of dementia presents characteristic regional metabolic abnormality, they may also resemble each other on F-18 FDG PET images. The other Nuclear Medicine studies can help to differentiate subtypes of dementia in difficult cases. For example, DAT scan can help differentiating AD from DLBD and other dementias with parkinsonism and amyloid PET imaging can help differentiating AD from FTD (32, 33). In DLBD and other dementias with parkinsonism, DAT scan shows reduced uptake in bilateral or unilateral corpus striatum. Extrapyramidal
symptoms are also observed in FTD and reduced DAT binding has also been reported (34). Amyloid PET is positive in AD but usually negative in FTD (35).

SUMMARY

F-18 FDG PET brain imaging is useful in patients with dementia and requires careful assessment of images. Currently, visual analysis of images provides more accurate results than SQ analysis. However, visual analysis is subjective and requires expertise and has limited value for detecting mild changes in the brain. Current SQ analysis programs have certain limitations, particularly suboptimal localization of brain areas and normalization of activity. SQ analysis programs can detect mild changes in lobes of the brain but are limited in small areas or areas in close proximity due to suboptimal selection of brain areas. Developing more efficient quantitative analysis programs is important for early and differential diagnosis of dementias.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.
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Sixty-year-old female with progressive cognitive decline. A- F-18 FDG PET images show marked hypometabolism in bilateral parietal, and temporal lobes and mild hypometabolism in bilateral frontal lobes. Preserved metabolism is seen in bilateral motor cortices, occipital lobes and basal ganglia. Findings are consistent with Alzheimer’s disease (AD). Note that PET Maximum Intensity projection (MIP) image better locates cerebral cortical hypometabolic regions in a 3-dimensional presentation. B- A commercially available SQ analysis program (SQ analysis 1: NeuroQ, Syntermed Inc., Atlanta, GA) shows reduced metabolism in bilateral frontals, posterior cingulate cortices, temporoparietal junctions, temporal lobes (more on right), and right visual associative cortex, and very mildly also in left basal ganglia (Blue: Normal metabolism. Red, pink and purple: Hypometabolism, red >-3 SD, pink >2-3 SD, and purple >1-2 SD). However, it does not show the marked hypometabolism in bilateral parietal lobes (superior and inferior) and underestimates the hypometabolism in left temporal lobe. Another commercially available SQ analysis program (SQ analysis 2: Hermes BRASS, Hermes Medical Solutions, Stockholm, Sweeden) provides more matching results with visual analysis in cerebral cortex but not in basal ganglia (Hypometabolism: SD >-2). Suboptimal registration is seen in various parts of the brain including caudate heads (white arrows) with this program.
FIGURE 2.
Seventy-one-year-old female with progressive dementia, visual hallucinations, parkinsonian features, clinically diffuse lewy body dementia (DLBD). A- F-18 FDG PET images demonstrate reduced glucose metabolism in bilateral occipital lobes involving primary visual cortices (arrows) and mild or questionable reduced metabolism in left medial frontal region and left temporal lobe. Findings are consistent with DLBD. B- SQ analysis-1 shows markedly reduced metabolism in bilateral visual cortices, cerebellum, and left posterior temporal lobe and mildly reduced metabolism in left parietotemporal region, frontal lobe and anterior cingulate cortex. Cerebellar uptake appears to be normal on visual analysis. This is likely due to suboptimal selection of cerebellum in SQ analysis-1, possibly erroneously including occipital lobes in the ROI for cerebellum. SQ analysis-2 underestimates reduced metabolism in bilateral occipital lobes (including visual cortices) and also shows reduced metabolism in right frontal and left temporal lobes.
FIGURE 3.

A- PET image registered with a template shows suboptimal registration (SQ analysis-2). Left posterior part of the brain is not symmetrical with the right and therefore is not completely within the region of interest (white arrow) which will cause erroneous hypometabolism in this region. Suboptimal registration is also seen in temporal lobes and caudate heads (white arrows). B- Reformatted patient image with SQ analysis-1.

A-
Patient  Normal template  Reformatted patient
FIGURE 4.
Basic diagramatic illustration of opening up cerebral cortical gyri into a flat area.
FIGURE 5.
A- Selected CT, F-18 FDG PET and PET/CT fusion images of the brain. Significant motion artifact causing artifactually reduced uptake in the left hemicortex (CT attenuation correction artifact). It is important to review PET/CT fusion images to better identify motion artifacts and not interpret as reduced metabolism. B- Anterior and lateral X-ray scout and PET/CT fusion images of the head in transaxial and sagittal views. Misplacement of region of interest box (green lines) on lateral scout X-ray images causing anterior part of the brain not to be imaged in a patient (top), and posterior part in another patient (bottom) during PET acquisition.

A-

B-
FIGURE 6.
FDG PET selected transaxial attenuation corrected (AC) and non-AC images of the brain shows reduced metabolism in left frontal and parietal lobes on both AC and non-AC images. Mildly reduced metabolism in right frontal and parietal lobes seen on AC images is not very apparent on non-AC images. Note that basal ganglia appears less intense on non-AC images due to higher attenuation of photons coming from deep subcortical structures.