Patterned Approach to Brain FDG PET Imaging in Dementia - Few Case Vignettes and Literature Review


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Introduction

Dementia, a disorder due to cognitive decline, results in impairment in attention, language, memory, executive function, social cognition and perceptual motor [1]. With the fast paced advancements in health care leading to prolonged life span and ageing communities, the elderly population at risk of dementia is increasing. The global estimate is expected to reach 66 million in 2030[2]. It is essential to identify primary neurodegenerative disorders early in the course. This becomes relevant in the current era of disease modifying therapies. With the current limitations of advanced structural imaging in early identification and differentiating primary neurodegenerative dementias, functional and molecular imaging plays a major role in filling the void. Functional imaging using PET can be performed using various ligands to assess dopamine metabolism, amyloid imaging, neuronal metabolism using 2-[18F] fluoro-deoxyglucose. Various ligands used in brain PET imaging are shown in (Fig 1). In this article, we discuss the experience of our center in Neuroimaging of dementia with special reference to FDG[3].

Decoding Image Acquisition in Brain FDG PET

Patient Preparation

A fasting of 4 hours prior to the procedure is required. Adequate hydration of the patient using intravenous fluids to enhance the renal elimination of the radioactive substance and voiding prior to the procedure to decrease contact time with the bladder is essential. Dextrose containing fluid should be avoided as it interferes with the FDG PET imaging. A glucose target of less than 140 mg/dl needs to be maintained. Drugs including but not limited to benzodiazepines, barbiturates and glucocorticoids which interfere with the uptake of the radioactive material should be avoided. However if sedation is required, benzodiazepines may be administered 30 minutes after the injection of the radioactive tracer prior to imaging. Substances such as alcohol, coffee, tea and nicotine should be avoided prior to the procedure. Patient should be in an awake state with the head held motionless and eyes open during the process of imaging[4].

Image acquisition and processing

Imaging is performed half hour after the injection of radioactive tracer. The total dose of the fluoro-deoxyglucose administered is approximately 3 MBq/ kg. Depending on the scanner, it may take approximately 15 minutes to perform the imaging. Images are acquired using appropriately positioned image acquisition cameras. The image acquired is processed and mapped onto the standard template of the brain comparable to Thalairach atlas, which consists of standardized images in the axial plane with matching of the corresponding voxel. Post-processing the grey scale images are color coded based on the standard deviation Z score, which is the measure of the number of standard deviations from the mean of the standard reference data. The voxel activity is normalized either globally or with respect to a particular reference point which is considered normal and least likely to be affected by the disease.
process. In the following case vignettes, global normalization was performed. The reconstructed images are presented for analysis using 3D stereotactic surface projection (SSP). Computed tomography (CT) imaging is also performed simultaneously for anatomical comparison. The analytical software employed in the following scenarios is Cortex ID, GE healthcare[5,6].

Case Vignettes

Case 1
A 39 year old female, homemaker by occupation married for a year with no known previous co-morbidities was brought with complaints of behavior and personality disturbances. The husband had sought consultations for increased sexual drive and increase in the frequency of meal consumption by the patient. The patient had craving for carbohydrates. The initial workup was negative for hepatitis B, hepatitis C, herpes simplex, syphilis and HIV. The initial MRI was normal. However, the symptoms were progressive over subsequent months. There was a lack of insight into the symptoms with progressive deterioration of personal hygiene. Family history was negative for any neurologic or psychiatric illnesses. Neuropsychiatric assessment revealed abnormal executive tasks and perseveration with preserved visuospatial tasks. Her spinomotor examination was normal. Carotid and vertebral artery Doppler was normal. Inflammatory markers including CRP were normal. Antibody profile for autoimmune rheumatological diseases was negative. Thyroid function test, serum vitamin B12 levels and serum homocysteine levels were normal. MRI brain revealed predominant atrophy of the frontal and temporal lobes. Her PET imaging revealed moderate to severe reduction in FDG uptake in bilateral frontal lobes and bilateral anterior temporal lobes(Fig 2). The hypo-metabolism was more prominent in the ventromedial frontal lobe. The patient was treated with aripiprazole for the sexual drive. However, the dementia progressed and the patient eventually died.

Case 2
52 year old female who was working as an office assistant was brought for neurologic consultation for progressive language disturbances for the past 2 years. The patient had difficulty in naming objects while conversing in the office. Initially she took longer to name objects and progressively was not able to do so and had to point at them. She also had noticed progressive difficulties in understanding the content of files in the office. Neuropsychiatric assessment had revealed a normal repetition, word output. However, she had difficulty in naming the objects, category naming.
circumlocution and intact comprehension for simple commands when asked to point objects. She was able to differentiate between left and right. Examination was negative for finger agnosia. She had intact executive function, visuospatial skills. Investigations for reversible causes of dementia including thyroid function test, serum vitamin B12, serum homocysteine levels were normal. Carotid and vertebral artery Doppler were normal. HIV, syphilis, Hepatitis B and hepatitis C were negative. MRI brain had revealed asymmetric atrophy of bilateral temporal lobes with predominant left side involvement. Brain PET-CT revealed asymmetric hypometabolism of bilateral temporal lobe involvement with severe left sided involvement and moderate right sided involvement. MR-PET fusion studies were performed, which showed decreased FDG PET uptake in bilateral temporal lobes (Fig 3). The left superior temporal gyrus was predominantly involved. The diagnosis was consistent with semantic variant primary progressive aphasia.

Case 3
A 73 year old male, a retired executive was brought neurology clinic to the neurologic clinics for tremor and difficulty in performing activities for the past 2 years. The patient complaints of shaking of both hands, difficulty in performing activities and sleep disturbances with increased day time sleepiness. On probing, he had acknowledged the occasional visualization of red ball in the corner of the field which did not annoy him. He had initially sought consultation and was started on levodopa-carbidopa. Six months prior to the onset of symptoms, he had noticed driving difficulties and had lost his way once. He was fined twice for skipping signals following which he had stopped driving. 8 months prior to the current presentation he was hospitalized for altered sensorium which lasted for 2 days, during which extensive investigations yielded negative results for the cause. Examination revealed symmetric, coarse tremor at rest and on action, bradykinesia and rigidity. Neuropsychiatric tests revealed impaired visuospatial functions evident from overlapping pentagons, clock drawing and impaired executive functioning evident from impaired luria three step test and go-no go test. Reversible causes of dementia evaluation revealed normal thyroid function test, serum vitamin B12 and a negative viral serology. MRI brain was normal. CT PET studies revealed decreased FDG uptake in right occipital cortex, left posterior cingulate cortex and posterior parietal association cortex (Fig 4). The above findings were consistent with a diagnosis...
of Lewy body dementia. Patient was treated with levodopa-carbidopa, donepezil and clonazepam.

Case 4

A 78 year old woman was brought by her husband with 5 year history of disturbances in memory. The husband had sought consultation for progressive deterioration in memory difficulties and difficulties in money handling by the patient. She also had progressive language difficulties in naming objects, word finding difficulties, difficulty in comprehending things spoken to her and impairment of executive functioning with poor organization of task and poor housekeeping. The patient also loses temper when pointed out at the deficit. Neuropsychiatric assessment revealed a global cognitive decline with poor performance in memory, visuospatial and impairment in testing for executive functioning and attention. Reversible causes of dementia were ruled out. MRI brain revealed diffuse cerebral atrophy with widening of sulcal spaces and prominent ventricles. PET CT image revealed profound hypo-metabolism in bilateral temporal and parietal lobes with moderate hypo-metabolism in bilateral frontal lobes. The findings were consistent with diagnosis of advanced Alzheimer's dementia. Patient was treated with a combination of memantine and donepezil and is on follow up (Fig 5).

FDG PET in Dementia

Dementia maybe caused by primary or secondary insult to the neuron. Secondary causes of dementia include structural lesions, vascular insults, hormonal and metabolic derangements, inflammatory and toxic cause. Ensuing the investigations for secondary dementia including but not limited to CT, Magnetic Resonance Imaging (MRI), metabolic and hormonal evaluation, the pertinence of structural imaging in the early diagnosis and differentiation of primary dementia becomes inconspicuous. Clinical evaluation and screening tests are not sufficiently sensitive in early detection in patients with higher cognitive reserve and may suffer significant cognitive decline before being recognized on standard neuropsychiatric tests. Functional imaging using FDG PET helps in the early diagnosis and differentiation of various primary dementias.

The radioactive tracer 18F-flurodeoxy glucose is taken by the
neuron and is phosphorylated by hexokinase. This helps in sequestering the tracer within the neuron and the degree of uptake is directly proportional to the metabolic activity of the neuron. The activity measured is high in the corpus striatum, thalamus and seconded by cortex in healthy individuals. The decrement in the metabolic activity is an indirect measure of the pathology in the affected region. Hence, decrement in degree of radioactivity provides a measure of the hypo-metabolism. Based on the pattern of hypo-metabolism obtained in the FDG PET, the probable etiology of the primary dementia could be deciphered. The relevance of such early detection becomes appropriate in the current era when disease modifying therapies are rapidly emerging, which requires administration early in the course of the disease for better efficacy. The area of hypo-metabolism as depicted by PET correlates clinically with the neuropsychiatric deficits. However, FDG PET is not pathology specific and does not represent the underlying pathological protein responsible for the disease manifestation[7,8,9,10].

**Patterned Approach to Brain FDG PET**

The hypo-metabolism measured using FDG PET indirectly measures the underlying pathology. It is essential to reiterate

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**Fig 5.** PET-CT image showing profound hypo-metabolism in bilateral parietal and temporal lobes with moderate hypo-metabolism in bilateral frontal lobes.
the fact that FDG PET is metabolism specific and not pathology specific. The pattern of involvement as depicted in the 3D SSP helps in deciphering the underlying etiology. The yield increases when used in conjunction with neuropsychiatric testing. The pattern involvement in each disease is discussed below.

**Alzheimer’s Dementia**

The initial deposition of amyloid in the medial temporal lobe manifests with memory impairment early in the course of the disease. Akin to the pathological deposition, hypo-metabolism in the medial temporal cortex predicts the development of Minimal Cognitive Impairment (MCI) in healthy individuals. The involvement of posterior cingulate cortex occurs early and is a highly sensitive measure of conversion from MCI to Alzheimer’s dementia. The posterior parietal, temporal association cortices, medial temporal lobe (including structures such as hippocampus and entorhinal cortex), precuneus are characteristically involved. The involvement may be asymmetric or unilateral. As the disease progresses, involvement of the prefrontal cortex becomes evident. Hypo-metabolism of the frontal lobe correlates with rapid cognitive decline in subjects with a good cognitive reserve. The pattern and degree of involvement evident in PET-CT correlates clinically as described in the case vignette 4 above. The anterior cingulate cortex, primary motor and sensory cortical strips, occipital cortex and the basal ganglia are spared in the disease. However, posterior pattern of hypo-metabolism with involvement of occipital cortex is evident in posterior cerebral atrophy variant of Alzheimer’s dementia[11,12,13].

**Dementia with Lewy Bodies (DLB)**

The hypo-metabolic signature seen in FDG PET in a patient with DLB is similar to Alzheimer’s disease with the involvement of posterior cingulate cortex, posterior parietal and temporal association cortex. The hypo-metabolism in occipital cortex and caudate nucleus seen in patients with DLB may help differentiate from Alzheimer’s dementia. The hypo-metabolism of primary visual cortex and posterior parietal involvement may predate clinical presentation and hence help in predicting future occurrence[14,15,16].

**Frontotemporal Dementia**

The fronto-temporal dementia is a wider entity with three subtypes under its hood. These include frontal or behavioral variant, temporal or semantic variant and non-fluent primary progressive aphasia. The brain FDG PET metabolic signature in classic fronto-temporal dementia includes hypo-metabolism in the frontal lobe, anterior temporal lobe and anterior cingulate cortex. The FDG PET demonstrates hypo-metabolism in the frontal cortex in frontal variant, anterior temporal lobe in temporal variant, frontal operculum in non-fluent primary progressive aphasia. The involvement of anterior temporal cortex in the absence of posterior temporal cortex favours the diagnosis of temporal or semantic variant of fronto-temporal dementia. MRI may detect predominant atrophy of the frontal and temporal lobes as mentioned in case vignettes 1 and 2. However, the PET-CT finding predates structural changes and aids in early detection. Hypo-metabolism may also be the only finding in more than half of the patients in whom structural imaging remains normal[17-20].

**Corticobasal Degeneration (CBD)**

CBD manifests with features involving basal ganglia and cortex. The clinical findings are mirrored in the brain FDG PET revealing hypo-metabolism in the basal ganglia, sensorimotor cortex and mid portion of the cingulate gyrus with extension into anterior and posterior cingulum. The involvement in the above mentioned areas are asymmetric akin to the asymmetric clinical manifestation. The posterior visual cortex and its association areas are spared[5,21].

**Vascular Dementia**

The findings on brain FDG PET in patients with vascular dementia
include well defined and circumscribed areas of hypo-metabolism confined to vascular territories. The structural imaging reveals encephalomalacia mirroring the metabolic changes. Hypometabolism in the frontal lobe may be accompanied by hypometabolism in the cerebellum contra laterally due to crossed cerebrolenticellar diaschisis (Fig 6)[22].

Combination Imaging Approach to Dementia

The hypo-metabolic signature in brain FDG PET may be overlapping in few of the diseases causing dementia. In such cases, pathology specific imaging may be useful such as dopamine transporter imaging and amyloid imaging. In patients with FDG PET suggesting either Alzheimer’s dementia or dementia with Lewy bodies, a normal dopamine uptake and positive amyloid imaging would suggest Alzheimer’s dementia, whereas decreased uptake in the basal ganglia and asymmetric involvement suggests dementia with Lewy bodies. Nevertheless, amyloid deposition may be positive in over 50% of the patients with DLB. Fronto-temporal dementia reveals a negative amyloid and normal dopamine uptake. However, this combination approach in the categorization of dementia is still considered investigational owing to increased false positivity's[23].

MRI/PET fusion imaging is a robust tool in the armamentarium of nuclear medicine. This combines the functional superiority of PET imaging with structural superiority and higher resolution of MRI and helps in delineating structures. Its wide spread use is limited by the longer duration of imaging that causes constraints and limitations on the technical expertise that is available for functional imaging. However, the advancements introduced by such fusion imaging are futuristic and exponential. It helps in ruling out structural lesions in the regions of hypo-metabolism, thus attributing the diagnosis to neurodegenerative diseases. In advanced stages of disease, it can help correlate the atrophy in structural imaging to the functional decline as established by hypo-metabolism. In structurally positive dementias, it helps in correlating the hypo-metabolism and also in detecting functional changes, if any, distant to the structural abnormality. The most common used radio-ligand in MR/PET fusion imaging is FDG, which measures the functional decline. The use of tracers that bind to the proteins such as beta amyloid, alpha synuclein, tau may be pathology specific. However, its use is limited by the lack of wide spread availability of the tracers. The diagnostic potential of the combination is further set to widen with the combination of pathology specific radio-ligand, which detects the protein accumulation that causes neuronal destruction and advanced sequences in MR imaging such as the arterial spin labeling sequences, which detects the consequence of the protein accumulation (Fig. 2)[24].

Red Herrings in Brain FDG PET

Patterns mimicking diseases can occur in the absence of dementia. A structural lesion such as cyst, if strategically located at the temporal pole would mimic a temporal variant of fronto-temporal dementia. Hence it becomes essential to review structural imaging of the brain imaged concurrently. Eye closure while imaging can reduce the metabolism in the occipital cortex which may simulate a posterior cerebral atrophy or DLB. The use of drugs such as benzodiazepines or barbiturates may reduce the uptake by as much as 20% globally and hence needs to be administered 30 minutes after the tracer. Evident atrophy in structural imaging may mimic hypo-metabolism, further reiterating the need for comparing a concurrent structural imaging[5,25].

Conclusion

The use of PET-CT has seen the gather of tremendous clinical data and wide spread use since its FDA approval in 2004. It helps in the early detection as early as in the pre-symptomatic stage, just when disease modifying strategies could pronounce a clinical difference in the current era. With the developments in the field of nuclear medicine and advanced radio-tracers being available and its combination with the MR imaging, the possibilities for advancements are prodigious.

References


