PETCT brain imaging in dementia

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Dr Haroon Motara
FY1, West Yorkshire Foundation Programme

Dr Chirag N Patel
Consultant radiologist and nuclear medicine physician

Dr Fahmid U Chowdhury
Consultant radiologist and nuclear medicine physician

Department of nuclear medicine and PETCT, Leeds Teaching Hospitals NHS Trust

Introduction
Dementia is a clinical syndrome characterised by neurodegeneration that leads to progressive deterioration in several intellectual domains, including memory, language and executive brain function. Alzheimer’s disease (AD) is the commonest cause of neurodegenerative dementia that accounts for more than 60% of all cases, followed by vascular dementia, mixed dementia, Lewy body dementia (DBL), frontotemporal dementia (FTD), and other rarer causes. The World Alzheimer Report projects that the number of people living with dementia worldwide will increase from 47 to 131 million by 2050 and will cost US$1 trillion by 2018. In the UK, there are over 850,000 people living with dementia with an estimated national economic cost of UK£26 billion.

Although dementia is considered an incurable condition, obtaining a timely diagnosis is crucial not only to allow access to appropriate treatments, but also to empower individuals to participate more actively in management decisions, plan for their future, and access support services from statutory and voluntary organisations. Failure to make a diagnosis can also potentially lead to long periods of follow-up and repeated neuropsychological assessments, which can have overlap with other causes, eg DLB. FDG imaging can show a very classical pattern of glucose hypometabolism in AD, which involves the associative temporo-parietal area, cingulate cortex, basal ganglia and cerebellum effectively defines the ‘metabolic phenotype’ of AD. The involvement of these areas, this phenomenon can be utilised clinically in patients with cognitive impairment where the precise diagnosis is unclear, eg during the earlier stages of dementia, in patients presenting at a younger age (<65 years of age), in those with atypical presentations, and in individuals who have substantial psychological overlay to their symptomatology.

Technique
Adequate patient preparation and cooperation are important, with a minimum fast of six hours and a capillary blood glucose <10mmol/l prior to tracer injection. Relevant aspects of mental capacity, safeguarding and informed consent as applied to this patient cohort must be considered when providing an imaging service of this type. A standard intravenous injection of 250MBq of FDG is followed by a 30-minute uptake period. The PET protocol used at the authors’ institution consists of a 10-minute single-bed acquisition with the head positioned in a suitable head restraint. The following image reconstruction parameters are used for the PET component: Time-of-flight algorithm (Vue Point FX, GE Healthcare), with iterative reconstruction involving 24 subsets, two iterations and a 3.2mm spatial filter. The CT part of the examination is achieved with the patient in the same position, using the following parameters: 125kV, 250mAs and 3.75mm section thickness. The use of a validated statistical parametric mapping (SPM) software brain package is considered mandatory for the interpretation of these scans, eg Cortex ID (GE Healthcare).

Alzheimer’s disease
Several longitudinal studies have shown that pathologically-proven AD can present with a range of symptoms and a variety of presentations. Therefore, it is not surprising that clinical diagnosis of AD can have an accuracy of <70%, and up to 50% of patients can remain undiagnosed until the later stages of the disease. FDG imaging can show a very classical pattern of glucose hypometabolism in AD, which involves the associative temporo-parietal area, cingulate gyrus and precuneus region (figure 1). The involvement of these areas, with lesser degree of abnormality in the frontal cortex and sparing of the primary visual cortex, sensorimotor cortex, basal ganglia and cerebellum effectively defines the ‘metabolic phenotype’ of AD. Predominant involvement of the occipito-temporo-parietal association areas may indicate the posterior cortical atrophy variant of AD, although this can have overlap with other causes, eg DBL.

There have been several studies over the last 15 years that have assessed the accuracy of FDG imaging in the diagnosis of AD. Silverman et al., in one of the largest multicentre studies of 284 patients, showed that PETCT had a sensitivity, specificity, and accuracy of 95%, 71% and 89% respectively. Many of these studies, however, involved heterogeneous patient cohorts, used different inclusion criteria, and applied different interpretative methodology. Bohnen et al used more stringent criteria and showed the accuracy of CT (SPECT) due to obvious practical advantages, including superior spatial resolution, less technical variation, shorter acquisition times, and an overall 15-20% increase in diagnostic accuracy.

"F-FDG PETCT brain imaging in dementia

The brain is an obligate glucose user for its metabolic requirements, and 18F-FDG imaging is an in-vivo non-invasive test that can be used to demonstrate regional cerebral glucose utilisation. As different causes of neurodegenerative brain disease preferentially involve certain brain regions, this phenomenon can be utilised clinically in patients with cognitive impairment where the precise diagnosis is unclear, eg during the earlier stages of dementia, in patients presenting at a younger age (<65 years of age), in those with atypical presentations, and in individuals who have substantial psychological overlay to their symptomatology.
FDG imaging in dementia ranged widely from 68-100% depending on the patient cohort studied. Diagnostic challenges can arise from phenotypical variants of AD, which can present with focal cortical syndromes without the classical amnestic symptoms of AD, such as frontal variant AD and logopenic aphasia. There can also be overlap with FTD in the clinical assessment as well as functional imaging patterns of FDG PET, with up to 10% of patients with either AD or FTD falling into this category.1

Within this context, the current authors recently conducted a ‘real-world’ study into the brain PETCT service for patients with cognitive impairment at their institution.2 A retrospective evaluation of 136 patients, with a mean patient follow-up of 471 days, showed that FDG PETCT had an impact on patient management in 81%, adding confidence to the pre-test diagnosis in 43%, changing the pre-test diagnosis in 35%, reducing the need for further investigations in 42%, and resulting in a change in therapy in 32%. There was substantial correlation between the PETCT diagnosis and the final clinical diagnosis, with a correlation (k) coefficient of 0.78 (p<0.0001). The accuracy of FDG PETCT in diagnosis of AD was 94% (95% confidence interval [CI]: 87-99), with a sensitivity of 87% (95% CI: 75-92) and a specificity of 97% (95% CI: 87-99).

Other subtypes of dementia

There are recognised patterns of metabolic deficit in other subtypes of dementia such as FTD and its variants (figure 2), DLB, and rarer causes such as cortico basal ganglionic degeneration (CBG), progressive supranuclear palsy (PSP), and Parkinson’s disease dementia (PDD). These are summarised in table 1.

Non-FDG PET tracers

It is recognised that patients with dementia referred for advanced imaging may have a mixture of causal pathological factors, and this can make interpretation of FDG imaging very challenging.8-10 Even though FDG imaging may lack accuracy in certain situations, eg in the early stages of AD, Herholz and colleagues13 showed in a prospective study that those with possible/probable AD with mild cognitive impairment and a highly abnormal FDG examination have almost a five-fold risk of disease progression compared to those with mild metabolic changes or a normal study. The pathology of AD shows two main types of degenerative processes, while neuritic plaques, characterised by the deposition of β-amyloid, and neurofibrillary tangles involving tau-proteins. Both these biomarkers can now be imaged using 18F-labelled PET radiotracers. Although tau-imaging remains within the research domain at present,13 there is certainly an emerging clinical role for amyloid tracers such as florbetapir-18F, florbetaben-18F and flutemetamol-18F (figure 3),14-16 Clark et al17 compared in-vivo amyloid plaque imaging using florbetapir-18F to post-mortem evidence, showing a sensitivity and specificity of 92% (95% CI: 78-98) and 100% (95% CI: 80-100) respectively. These tracers could find a useful diagnostic role in a sub-group of patients with suspected AD, eg in younger patients and in those with progressive symptoms of dementia but normal or equivocal FDG imaging. Although amyloid PET tracers are now recommended for clinical use in highly selected patients by evidence-based guidelines, they are still not routinely commissioned or reimbursed by the National Health Service in England (NHSB).18

Conclusion

Traditionally, neuroimaging in dementia has been used to exclude structural causes of cognitive impairment. The emphasis of modern AD imaging guidelines is progressively shifting towards a ‘triangulated’ and personalised approach, utilizing biomarkers that will influence diagnosis, prognosis and therapy.19 FDG and non-FDG PET radiotracers in brain imaging are being increasingly recognised as important biomarkers of AD, and their role in the management of this hugely important condition will undoubtedly expand in the future.

References

Figure 1
(A) Axial and sagittal FDG PET images, axial low dose CT, and fused axial PETCT image. This case shows symmetric hypometabolism in the parietal lobes, extending into the cingulate gyri and precuneus areas (arrows) in the characteristic pattern of metabolic deficit that is seen in AD. (B) SPM analysis using Cortex ID confirms these regional areas of hypometabolism.

Figure 2
(A) Axial and sagittal FDG PET images, axial low dose CT, and fused axial PETCT image. This case shows bilateral frontal lobe hypometabolism (arrows) in a patient with behaviour-variant FTD. (B) SPM analysis using Cortex ID confirms these regional areas of hypometabolism.
**Figure 3**
Selected axial images from an 18F-Florbetaben PET study show loss of grey-white matter differentiation and marked cortical uptake of tracer in the parietal, frontal, and temporal cortex. The findings are in keeping with pronounced β-amyloid deposition in AD.

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<th>Disease</th>
<th>Typical brain regions demonstrating hypometabolism on FDG PET imaging</th>
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| AD      | **Early disease:** Parietal lobes (including the precuneus), temporal lobes (including the hippocampus), posterior cingulate gyrus  
          **Advanced disease:** Frontal lobes (prefrontal cortex) |
| FTD     | **Behaviour variant:** Frontal and anterior temporal cortex, anterior cingulate gyrus  
          **Semantic variant:** Anterior temporal deficit predominates, often asymmetric  
          **Logopenic variant primary progressive aphasia (PPA):** Left-dominant posterior temporal and parietal  
          **Non-fluent agrammatic PPA:** Inferior frontal, temporo-parietal junction and left peri-Rolandic gyrus |
| DLB     | Parietal and temporal lobes with significant metabolic reductions in the occipital lobes |
| CBGD    | Asymmetric sensorimotor cortex, fronto-parietal, basal ganglia |
| PSP     | Mid-brain, caudate, frontal lobes |
| PDD     | Similar to AD |

**Table 1**
Typical patterns of hypometabolism on FDG PET imaging of the brain in different neurodegenerative conditions that are associated with cognitive impairment and dementia.