**Amyloid brain PET imaging**

RAD Magazine, 43, 506, 15-17

**Nick Gulliver**
Chief clinical technologist

**Dr Nicola Mulholland**
Consultant radiologist and nuclear medicine physician

**Dr Gill Vivian**
Consultant radiologist and nuclear medicine physician

Department of nuclear medicine and PETCT,
King’s College Hospital NHS Foundation Trust, London
kch-tr.nucmedreferral@nhs.net

**Introduction**

Brain positron emission tomography (PET) has also been used over many years to diagnose neurodegenerative diseases, and has advantages over MRI due to its higher sensitivity to detect pathologies at a molecular level. While 18F-fluorodeoxyglucose (FDG) PETCT is an established imaging technique for assisting in the differential diagnosis of Alzheimer’s disease (AD) and other forms of dementia, PETCT imaging using beta-amyloid plaque avid tracers has only recently come into clinical use in the UK, having been a subject of intensive research and development in recent years. This review briefly describes the principles and practice of amyloid brain PET imaging, including image acquisition, image interpretation and future developments.

**Dementia, Alzheimer’s disease and mild cognitive impairment**

It has been estimated by the Alzheimer’s Society that dementia in the UK costs the UK economy around £23.6 billion per year. Dementia is the fourth leading cause of death in individuals over 65 years of age in the UK. It mainly affects men and women over 65 years of age, with risk increasing with age. AD is the most common cause of dementia in the elderly (accounting for 50-60% of dementias). The Alzheimer’s Society estimates 850,000 people in the UK have dementia and projects that this will have increased to over one million by 2025 and over two million by 2051.¹

Like most dementia types, neuropathologic causes of AD is related to proteinopathy. A definitive diagnosis of AD requires both a finding of clinical symptoms and evidence of neuropathology such as beta-amyloid (Aβ) plaques. Histopathologic analysis at autopsy remains the standard of reference for the diagnosis of AD. AD is characterised by neuronal cell loss due to formation of two different insoluble protein aggregates – extracellular Aβ plaques (which consist of aggregated Aβ protein) and intracellular neurofibrillary tangles (which consist of aggregates of hyperphosphorylated tau protein).

Deposits of Aβ are also present in other neurodegenerative diseases associated with dementia, such as Parkinson’s disease and dementia with Lewy bodies. Thus amyloid PET is not helpful in differentiating these two dementia types.

However Aβ deposition is not a feature of frontotemporal dementia (FTD) so amyloid PET has a role to play in differentiating FTD from AD.

Aβ plaque build-up appears to be an age-dependent process as, while amyloid is present in up to 20% of healthy 65-year-olds, it can be found in 85% of those over the age 85 years. Current models of the neurodegenerative process indicate that Aβ plaque build-up is slow and precedes cognitive impairment and brain atrophy. Also, at any given time amyloid PET abnormality is more marked than MRI and FDG PET abnormality² (figure 1).

Mild cognitive impairment (MCI) or “prodromal” AD is a condition where memory is impaired but which does not meet the criteria for dementia, and can precede the onset of dementia for many years. MCI is usually diagnosed clinically with a mini mental state examination or similar clinical evaluation to measure cognitive impairment. However, clinical assessment alone has a low sensitivity and specificity.³ Having MCI does not always indicate progression to dementia, although over half of all patients presenting with MCI will develop dementia within five years.⁴ AD usually begins with cognitive symptoms (particular memory loss) followed by non-cognitive symptoms (relating to behavioural and psychological conditions).

Currently there are no disease-modifying treatments for AD, although there have been promising results published that indicate that a disease-modifying drug may be just around the corner. Current treatment for AD is to reduce symptoms of the disease but does nothing to modify the pathological process and is not curative.

**Available amyloid plaque tracers**

The first Aβ plaque tracer to be developed was 11C-PiB (Pittsburgh Compound B) in 2004. A radiolabelled derivative of thioflavin (a fluorescent dye used by pathologists to identify plaques in brain tissue specimens) which selectively binds to amyloid plaque and cerebrovascular amyloid, 11C-PiB imaging spread rapidly to academic centres worldwide but its short half-life of 20 minutes has limited its widespread clinical use. This was followed a few years later by the development of 18F-labelled tracers: 18F-florbetapir (Amyvid, Eli Lilly), 18F-fllobetaben (Neuraceq, Piramal) and 18F-flutemetamol (Vizamyl, GE Healthcare). Initial clinical comparison of 18F-Florbetapir PETCT and 18F-FDG PETCT in patients with AD and controls demonstrated increased sensitivity and specificity of florbetapir PETCT (95% and 95% respectively) compared to FDG PETCT (80% and 86% respectively).⁵ All three tracers now have approval from the USA FDA and European Medicines Agency. Each of these fluorinated Aβ plaque tracers has slightly different properties although the mechanism of uptake is the same. Recent systematic review showed no marked differences in diagnostic accuracy of the three Aβ plaque tracers currently available clinically in the UK.⁶,⁷

**Patient preparation and scan acquisition**

Unlike FDG, amyloid imaging agents are not susceptible to changes in metabolism, so patients do not have to fast before their appointment and may eat and drink after administration of the radiopharmaceutical. Furthermore, there is no requirement to stop certain medications (eg insulin or metformin). Similarly, patients do not need to avoid exercise or muscular activation before or after injection. In contrast to FDG brain PET imaging, standardisation of ambient conditions (warm uptake room with reduced lighting and noise) is not required for amyloid PET imaging.

Although many patients undergoing amyloid PET at MCI stage may have few symptoms, clinical practitioners (radio-
graphers, technologists and nurses) should be aware of the most commonly experienced symptoms in order to provide better care to patients within the imaging environment. Patients with MCI or AD may need extra support from family members when attending imaging departments, frequent reassurance and repeat instructions.

The clinical value of amyloid PET imaging is entirely dependent upon the quality of the images and accuracy of interpretation. The delay from injection to scan acquisition is based on achieving maximal contrast between cortex and reference region. Following this uptake period (ranging from 40 to 90 minutes depending on which tracer), a single PET bed position of 10-20 minutes (in list mode in order to mitigate any potential motion artefacts) is acquired, with the patient lying supine and cantoaxial line perpendicular to z-axis in order to ensure that axial slices through the brain are standardised and with minimal yaw or roll to ensure axial slices are symmetric. In some instances, a family member or caregiver may be enlisted to encourage the patient to remain still with optimum positioning during the image acquisition.

**Scan interpretation**

Although image display for interpretation varies between florbetapir, florbetaben and flutemetamol, essentially all three scans are interpreted the same – assessment of cortical grey matter contrast relative to white matter, using a binary read methodology. A negative scan shows normal preserved contrast with cortical SUV less than adjacent white matter. Negative scans show sparse or no Aβ plaques which is inconsistent with a diagnosis of AD. A positive scan shows reduced contrast between cortical grey matter and adjacent white matter, with Aβ binding extending to the outer edge of the brain (figure 2).

A positive Aβ scan does not independently establish a diagnosis of AD or other cognitive disorder since it can be present in other neurologic conditions and may be present in older people with normal cognition. Each of the Aβ tracers have manufacturer recommendations for the interpretation criteria for distinguishing negative/positive status (table 1) and extensive image reader training programmes are now widely available for each tracer. Difficulties in interpretation arise with noisy images and when there is a high degree of cortical atrophy. Co-registered CT or MR images provide additional information when there is uncertainty regarding location or edge definition of cortical grey matter and false negative occurrences can be reduced by examining structural images. A major limitation of amyloid PET to support a diagnosis of AD dementia is the high degree of motion blurring. Co-registered CT or MR images provide additional information when there is uncertainty regarding location or edge definition of cortical grey matter and false negative occurrences can be reduced by examining structural images. A major limitation of amyloid PET to support a diagnosis of AD dementia is the high degree of motion blurring.

Although not clinically used widely, quantitation of amyloid brain PET images (as an adjunct to visual interpretation) is now available via several packages available commercially including BRASS (Hermes Medical Solutions) and CortexID (GE Healthcare). These quantitation packages utilise voxel-based statistical analysis, such as three-dimensional stereotactic surface projections (3D-SSP) and statistical parametric mapping (SPM) software, to provide standardised, objective and quantitative validation of observed changes which allows calculation of SUVR (regional cortical standardised uptake value), a value of regional SUV compared to a reference region (cerebellum or pons), giving the reader additional confidence in the binary read, especially useful in equivocal cases 10,11 (figure 3).

**Other neurological PET applications for Aβ plaque tracers**

There is active research currently in using Aβ plaque tracers in brain conditions including cerebral amyloid angiopathy and traumatic brain injury. Several cases have been reported of the use of amyloid PET in Down’s syndrome and multiple sclerosis, although current evidence is limited.12

**Current and future status in the UK**

Amyloid brain PET imaging is now included in the evidence-based indications for PETCT in the UK published by the Royal College of Radiologists and Royal College of Physicians, and a number of centres including King’s College Hospital offer these scans clinically. Typically, amyloid brain PET services have been established in institutions with dementia specialism and expertise, in agreement with community memory clinics.

Appropriate use criteria for amyloid brain PET with Aβ plaque avid tracers is currently limited to:

1. Patients with persistent or progressive unexplained mild cognitive impairment (MCI)
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation
3. Patients with progressive dementia and atypically early age of onset, eg 50-65 years and possibly even younger.

Conversely, amyloid imaging is inappropriate in numerous situations including (but not limited to) for use in patients with core clinical criteria for probable Alzheimer’s disease with a typical age of onset; for determining dementia severity; for reasons of family history; or for non-medical usage (eg legal/insurance).13

Despite the inclusion of amyloid PET in the most recent commissioning policy statement, commissioning guidance from NHS England remains hesitant about NHS funding.15 This, and the fact that Aβ tracers are in the region of five to eight times the price of a dose of FDG, may have had some influence on the lack of widespread clinical availability of amyloid PET in many centres in the UK. Within a few years the results of a large-scale, longitudinal cohort study currently open in the US – the IDEAS study16 with the primary hypothesis that, in diagnostically uncertain cases, knowledge of amyloid status as determined by amyloid brain PET scanning will lead to significant changes in patient management and will translate into improved medical outcomes – may improve the accessibility of Aβ imaging in the UK.

**Conclusion**

Amyloid brain PET imaging is now in clinical use for identifying patients at higher risk for cognitive decline in the ageing population and mild cognitive impairment subjects. A positive PET amyloid scan does not provide a diagnosis of AD without other clinical measures for AD, partly due to the common finding of asymptomatic amyloid deposition in elderly patients. This has led researchers to change the question: “Why do people with AD have plaques?” to “Why don’t all people with plaques have AD?”17 It is expected that in future, longitudinal Aβ imaging studies will confirm the stages of Aβ deposition over time, contributing to the early and differential diagnosis of neurodegenerative conditions, and will likely be used for disease staging and as predictors of cognitive decline and disease progression. It is being used for both patient recruitment and outcome measure in current anti-Aβ therapeutic trials. Provided it is both accessible and affordable, amyloid brain PET imaging is likely to play an increasingly important role in clinical practice for the foreseeable future.

**References**


<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Colour scale</th>
<th>GM-WM findings</th>
<th>Threshold region</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-florbetapir</td>
<td>Black on white</td>
<td>Loss of GM-WM contrast because of increased GM uptake</td>
<td>Larger than a single gyrus</td>
</tr>
<tr>
<td>18F-florbetaben</td>
<td>White on black</td>
<td>Increased GM uptake extending to the cortical margin</td>
<td>Four cortical regions</td>
</tr>
<tr>
<td>18F-flutemetamol</td>
<td>Colour (rainbow or Sokoloff)</td>
<td>Increased GM uptake or loss of GM-WM contrast or both</td>
<td>Four cortical regions and one sub-cortical region</td>
</tr>
</tbody>
</table>

**TABLE 1**
Interpretation criteria for FDA/EMA approved amyloid imaging radiotracers (taken from Mallik A et al11).

---

**Figure 1**
Hypothetical model of Alzheimer’s disease histopathology and biomarkers (taken from Jack C et al1).

---

**Figure 1**
Hypothetical model of Alzheimer’s disease histopathology and biomarkers (taken from Jack C et al).
Figure 2
Transaxial PET slices. (A) Normal scan result showing distinctive pattern of retention in white matter, scan is negative for abnormal Aβ deposition and is not consistent with a diagnosis of AD; (B) Positive scan with uptake in cortical grey matter obscuring normal white matter pattern with binding extending to outer edge of brain (data from King’s College Hospital).

Figure 3
Example of 3D surface reprojection of Aβ abnormality using Hermes BRASS software (data from King’s College Hospital).