Beta-amyloid PET imaging for Alzheimer’s dementia diagnosis

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Alzheimer’s dementia is the most commonly diagnosed dementia. Despite this, diagnosis can be especially complex in certain circumstances. Any additional, novel diagnostic aids can positively add to the diagnostic process, overall accuracy and ultimately to patient care and treatment. Beta-amyloid (Aβ) positron emission tomography (PET) imaging is utilised as an important diagnostic tool in NHS dementia research in the UK and worldwide. Aβ PET imaging is now licensed for clinical use in the UK. This review explores the potential for the use of Aβ PET imaging in clinical practice highlighting recent evidence base followed by a discussion of potential benefits in the context of important clinical and practical considerations.

Alzheimer’s dementia (AD) is a chronic, progressive neurodegenerative disorder characterised by a global, irreversible impairment in cerebral functioning and is the most common type of dementia. Established criteria for the diagnosis of probable AD include the International Working Group-2 (IWG-2) diagnostic criteria and the Diagnostic and Statistical Manual of Mental disorders, 5th Edition. Definitive diagnosis can only be made post-mortem by histopathological examination. Known pathologies in AD include intracellular neurofibrillary tangles (NFTs) and extracellular Aβ plaques. Despite these helpful criteria, accurate diagnosis of AD can present challenges in certain circumstances. These circumstances could, for example, include patients with possible AD, equivocal investigation results and:

1. Atypical presentation (approximately 11% of AD cases), e.g. symptoms suggestive of posterior cortical atrophy or frontal variant AD.
2. An unusually rapid course.
3. Unusual presentation with complicating comorbid physical or mental health problems.
4. An atypical, very early onset dementia.

Any additional novel diagnostic aids with good sensitivity and specificity, which can positively add to the diagnostic process, diagnostic accuracy and to patient care and treatment are welcome. It is essential that any new diagnostic aids would be acceptable to patients, safe and also cost-effective. As there is no single test for AD, the condition is currently diagnosed using information including the patient’s history, collateral history from a relative/carer and cognitive testing (including at times more detailed neuropsychological testing). Physical examination and investigations including blood tests and neuroimaging such as computerised tomography (CT) or magnetic resonance imaging (MRI) brain are important in ruling out physical pathology. CT and MRI may also identify temporo-parietal atrophy, especially medial temporo/ hippocampal atrophy in AD. Less commonly, more detailed neuroimaging such as 99m Tc-hexamethylpropyleneamine oxime single-photon emission computed tomography (HMPAO SPECT) or fludeoxyglucose- (FDG) PET brain may be helpful in identifying focal hypoperfusion or hypometabolism in the temporo-parietal cortices. The recently updated National Institute for Health and Care Excellence (NICE) guidance from 2018 recommends the use of at least one structural image of the brain as part of the dementia diagnostic evaluation unless dementia is established and the subtype is clear. NICE also recommends that if the diagnosis remains uncertain and AD is suspected, further neuroimaging (SPECT or FDG-PET) or cerebrospinal fluid (CSF) examination should

<table>
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<tr>
<th>RCTU score</th>
<th>Condition for assessment</th>
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<tbody>
<tr>
<td>1 (No tracer uptake)</td>
<td>Tracer uptake (signal intensity) in grey matter is lower than in white matter.</td>
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<tr>
<td>2 (Moderate tracer uptake)</td>
<td>Smaller area(s) of tracer uptake equal to or higher than in white matter: extending beyond the white matter rim to the outer cortical margin involving the majority of the slices within the respective region.</td>
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<tr>
<td>3 (Pronounced tracer uptake)</td>
<td>A large confluent area of tracer uptake equal to or higher than that present in white matter extending beyond the white matter rim to the outer cortical margin.</td>
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Note: For a score of tracer uptake in the cortex, the finding should have been present in the majority of the slices within the region in question.
be considered. However, CSF examination is invasive and not often practicable in old age psychiatry-run memory services. However, with the advent of Aβ PET imaging, there is now an additional diagnostic modality that could positively impact on diagnostic accuracy in certain circumstances.

**Beta-amyloid**

Aβ is a protein created by cleavage of amyloid precursor protein (APP) by the sequential activity of the enzymes β-secretase and γ-secretase. Depending on the nature of the cleavage sites, various Aβ peptides are created, the lengths of which may vary. The Aβ42 peptide is thought to be the most likely to aggregate into neurotoxic oligomers and later into fibrils. This results in Aβ plaques, which are found in all cases of AD. Aβ plaques are thought to develop years before the clinical manifestations of AD become apparent – roughly 15 years before expected symptom onset. Aβ is most commonly deposited in the following areas: frontal lobes, lateral temporal lobes, parietal lobes and the posterior cingulate/precuneus areas.

**Aβ PET imaging**

Aβ PET imaging has transformed clinical AD research. This imaging is frequently used in AD clinical treatment trials as essential to confirm AD pathology. A negative Aβ PET is generally an exclusion criterion for AD clinical treatment trials of anti-Aβ monoclonal antibody investigational products. In clinical practice, Aβ PET imaging has been used more in recent years as an aid to AD diagnosis in certain cases, especially in the US. Amyloid imaging has been approved since 2012 by the US Food and Drug Administration (FDA) for help in diagnosing AD, but not for risk assessment. Aβ PET imaging is frequently used in the UK in NHS AD clinical treatment trials, it is utilised infrequently in clinical practice. In 2016, the Royal College of Radiologists and Royal College of Physicians recommended that Aβ PET imaging is only advised in highly selected patients with cognitive impairment where:

- AD is a possible diagnosis but this remains uncertain after comprehensive evaluation by a dementia expert and conventional imaging work-up.
- Knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and influence patient management.

There are several radiopharmaceutical diagnostic agents which can be used with PET imaging in AD. Two examples of these are:

- NeuraCeq or florbetaben (18F) (Piramal), and
- Amyvid or florbetapir (18F) (Eli Lilly)

Of Amyvid and NeuraCeq, only NeuraCeq is available for clinical use in the UK, whereas Amyvid is available for research purposes. NeuraCeq and Amyvid are both solutions for injection containing their respective diagnostic agent. Both radiopharmaceuticals bind to cerebral Aβ plaques. The low-dose radiation emitted enables detection of amyloid on PET imaging. In the UK, training with further assessment is required for an appropriate medical practitioner to be approved to read Aβ PET imaging. The Neuraceq Summary of Product Characteristics, for example, details how the PET images should be read/interpreted:

PET images are read in a transaxial orientation using a grey scale and should be read in a systematic manner, starting at the level of the cerebellum, then through the lateral temporal and frontal lobes, the posterior cingulate cortex/precuneus and finally to the parietal lobe. Interpretation of the images is made visually comparing the activity in cortical grey matter with activity in adjacent cortical white matter. Each of these brain regions, the lateral temporal, frontal, posterior cingulate, precuneus, and parietal lobes, should be systematically visually assessed and scored according to the regional cortical tracer uptake (RCTU) score (Table 1).10

The interpretation of the visual PET scan assessment is based on a binary outcome as ‘positive’ or ‘negative’. A negative scan (for an example see Figure 1) indicates sparse or no amyloid plaques meaning the patient is unlikely to have an AD diagnosis. A positive scan (for an example see Figure 1) is not confirmatory for AD as a
positive result may also occur with other neurological conditions and in older people with normal cognition. This binary classification differs from the qualitative reporting clinicians are more familiar with (eg with MRI and SPECT reports). In some cases, a binary outcome may be more challenging to produce. However, the result can be used together with clinical assessment to enable more accurate diagnosis of AD, especially in more challenging cases.

Evidence-based examples

**NeuraCeq (florbetaben [18F])**

A large multicentre, non-randomised phase 2 trial of 155 adults greater than 55 years of age with blinded PET readers concluded that visual assessment of the PET scans provided 80% sensitivity and 91% specificity in discriminating patients with AD from healthy controls. No safety concerns were noted.11 In a longitudinal study, 45 subjects clinically diagnosed with mild cognitive impairment (MCI), underwent baseline florbetaben ([18F]) PET scans and were followed for 24 months to evaluate the relationship between florbetaben ([18F]) imaging and changes in diagnostic status.11 MCI is defined as a condition where there is:

1. A change in cognition recognised by the affected individual or observers
2. Objective impairment in one or more cognitive domains
3. Independence in functional activities, and
4. Absence of dementia.12

Twenty nine (64%) MCI patients were positive by florbetaben ([18F]) PET scan. At the 24-month follow-up, 19 (42.2%) converted to clinical AD. Of the 29 MCI subjects who had a positive PET scan, 19 (65.5%) were classified clinically as converted to clinical AD after 24 months compared with 0 (0%) of 16 who had a negative scan. Sensitivity of the florbetaben ([18F]) scan to show the MCI conversion rate to AD in 19 converters was 100% and specificity in 26 non-converters was 61.5% (95% CI: 42.8-80.2%).

A systematic review of florbetaben ([18F]) PET scans for the early diagnosis of Alzheimer’s disease dementia in people with MCI analysed a four-year study with 45 participants with MCI.13 The median age was 73.5 years old for those with a PET-positive scan and 71.8 years old for those with a PET-negative scan. Florbetaben ([18F]) PET scan, as a single test with visual assessment, correctly classified 100% of the participants who progressed to AD and 83% of the participants who did not progress to AD at four years follow-up. The review concluded that florbetaben ([18F]) imaging is a promising test to predict the progression from MCI to AD. No recommendation was made by the authors based on the single study.

The most common side-effects with Neuraceq are pain, irritation and reddening of the skin at the site of injection (up to 10% of people). Other side-effects are uncommon, eg headache, hypotension, nausea, rash (0.1% to 1%).16

**Amyvid (Florbetapir [18F])**

A study analysed the sensitivity and specificity of amyloid PET imaging with neuropathology at autopsy.14 Fifty-nine participants had autopsies completed to prove significant brain Aβ plaques and the autopsy results were compared with the PET scan data. The PET scans had a sensitivity of 92% (36 of 39) and a specificity of 100% (20 of 20) in people who had autopsy within two years of PET imaging (the primary outcome). Essentially, the florbetapir ([18F]) PET scans were used to correctly identify 92% of the participants who had significant amounts of Aβ plaques as positive and all participants without significant plaques were correctly rated as negative.

A systematic review evaluated the accuracy of the florbetapir ([18F]) PET scan in identifying people with MCI who progress to AD over a period of time. The review looked at two studies that evaluated the progression from MCI to AD. One study had 401 participants with a follow-up of 1.6 years (mean age 72 years). The other study had 47 participants with a follow-up of three years (mean age 72 years). At 1.6 years, using visual assessment, the scan correctly classified 89% of participants who progressed to AD and 58% of participants who did not progress to AD. This indicated a low false negative though higher false positive rate. In the three-year study, which used visual assessment, the scan correctly classified 67% of people who progressed to AD and 71% who did not progress to AD. It was concluded that florbetapir ([18F]) PET scans could not be recommended for routine use in clinical practice to predict the progression from MCI to AD based on the available data at the time. Some limitations of the review were that findings were based on a limited number of studies and clarity was needed on whether scan information was assessed separately from the final diagnosis. Further studies were suggested.

The most commonly reported side-effects with Amyvid were headache (1% to 10%) and in 0.1% to 1%; musculoskeletal pain; increased blood pressure; nausea, rash, and injection site reaction.15

**Discussion**

Diagnosing AD may present challenges with certain clinical presentations. Further means of improving diagnostic accuracy are required. Until recently, only
autopsy enabled cerebral amyloid plaques to be confirmed for diagnostic purposes. Aβ PET imaging now allows amyloid plaques to be visualised ante-mortem. Despite this, Aβ PET scanning is used infrequently in clinical practice.

The EMA concluded that the diagnostic benefits of Aβ PET imaging outweighed risks. PET scans with Amyvid were reported by the EMA to have high sensitivity and specificity for detecting β-amyloid plaques in the brain with a good safety profile and non-invasive nature. The committee noted PET scans with Amyvid as a significant improvement in the diagnosis of patients with memory problems who are being evaluated for AD. The Committee recommended that Amyvid be given marketing authorisation throughout the EU in 2013.16

Neuraceq has received similar EU marketing authorisation. The EMA CHMP decided that Neuraceq’s benefits were greater than its risks and recommended that it be approved for use in the EU.17 Results from the main study analysed demonstrated that PET scans with Neuraceq have high sensitivity and specificity for detecting β-amyloid plaques in the brain. This is regarded as a significant improvement in the diagnosis of patients with memory problems who are being evaluated for Alzheimer’s disease and other types of dementia. However, due to a risk of false positive results, the EMA recommended that Neuraceq should not be used as the sole diagnostic method for dementia, but in conjunction with clinical evaluation.

In addition, the IWG-2 revised diagnostic criteria for typical and atypical AD advise that, together with the clinical AD phenotype, there should be evidence of one out of three in vivo examples of AD pathology. One of these in vivo criteria is increased tracer retention on Aβ PET imaging. The other two criteria are decreased Aβ1–42 together with increased tau in CSF and an AD autosomal dominant mutation being present (eg APP, PSEN1).

A group of experts also met to discuss Aβ PET imaging and published their recommendations.18 They suggested that these scans should be used clinically when the results would make a difference in treatment. According to the group, patients whose treatment might be changed in a helpful way by a PET amyloid scan result include:

1. Patients with persistent or progressive and unexplained MCI (or mild neurocognitive disorder).
2. Patients diagnosed with possible AD but with unusual features such as rapid course, unexpected symptoms or concurrent medical issues.
3. Patients with unusually early onset of dementia who might benefit from different treatment or from referral to a clinical trial on the basis of a scan result.

On the other hand, the consensus group discouraged use of amyloid imaging for patients whose management would not be likely to benefit, including:

1. Patients with typical AD symptoms, age of onset, and course.
2. Patients without symptoms or whose symptoms are not confirmed by clinical examination.
3. Patients seeking to know their risk for AD because of various concerns, including family history of dementia or presence of a particular version of the ApoE gene, or patients with a strong family history of early-onset AD seeking an alternative to gene testing.

Some NHS Trusts have also devised criteria for Aβ PET referral, for example, requiring that: referrals only come from a consultant-led memory service; patients have progressed through the full memory service assessment pathway including relevant structural imaging, and there is triage by the lead memory service consultant and lead radiologist.19

The criteria described may provide a sensible framework for the consideration of Aβ PET imaging in clinical practice.

Overall, are the benefits of Aβ PET imaging greater than the possible drawbacks? Potential advantages of Aβ PET imaging are illustrated by the generally good sensitivity and specificity (although there are a limited number of studies) and the fact that it is a minimally invasive investigation with a good safety profile. Other biomarkers such as lumbar punctures (LPs), for example, used to determine CSF Aβ and tau proteins, are generally more uncomfortable for patients. The EMA and FDA published favourable opinions on certain Aβ PET imaging for AD diagnosis after a detailed review process. Aβ PET imaging is frequently and successfully used for dementia diagnosis in dementia treatment research trials worldwide. Training is available to enable Aβ PET imaging reader proficiency. Over time the cost of Aβ PET imaging will likely continue to decrease, making this diagnostic aid more accessible in clinical practice.

Possible drawbacks to consider include the fact that Aβ PET imaging is invasive, though minimally so compared with investigations such as LPs. Adverse reactions are possible as outlined previously. Aβ PET imaging is also relatively expensive, costing anywhere from approximately £1000–£3000 per scan.20 Training for appropriate clinicians followed by assessment is required to become proficient at assessing Aβ PET
scans though training is also required for other biomarker investigations such as LPs. In addition, a Cochrane review found that the usefulness of Amyvid, for example, in predicting the development of AD in patients with MCI or in monitoring patients’ response to treatment has not been established.

On balance, Aβ PET imaging may be an appropriate adjunctive AD diagnostic biomarker for very selective use in more complex cases where, for example, confirming AD diagnosis may benefit the patient. As always, involvement of the patient and/or carer in making a fully informed decision will be essential.

Conclusion
In the UK, dementia-related diagnostic Aβ PET imaging is predominantly conducted in clinical research trials. Aβ PET imaging is seldom used in routine clinical practice for AD diagnosis. Expert opinions and suggested guidance on the potential clinical role of Aβ PET scanning in AD diagnosis have been published in recent years. A general theme from much of this advice suggests that these scans should only be used clinically when the results would make a difference in treatment for certain groups of patients. Aβ PET imaging may be of occasional assistance in evaluating persistent or progressive unexplained neurocognitive disorder and possible atypical early or later onset AD where there is ambiguity. Some UK NHS Trusts have limited access to Aβ PET scanning on a special request basis where there may be a clear benefit. Expert groups such as the EMA CHMP are clear in not recommending Aβ PET imaging for routine dementia diagnostic use. It appears reasonable for Aβ PET imaging to be used very selectively and not universally, as routine clinical assessment is sufficient for providing a diagnosis for the vast majority of patients with AD. Cost is an important consideration for clinicians though cost is likely to decrease over time.

It is advantageous for clinicians to be aware of Aβ PET imaging as a diagnostic aid as it has the potential to be valuable to patient assessment and diagnosis, facilitating earlier and tailored treatment and care, which may improve clinical outcomes in some cases. Even if Aβ PET imaging is not currently available to all clinicians, it may become more available over time. Knowledge of this diagnostic aid is therefore useful. Further good quality evidence together with clear guidelines on usage would aid clinician consideration of Aβ PET imaging in clinical practice.

Declaration of interests
Dr Byrne has previously received speaker honoraria from Eli Lilly.

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References