Review ❚ Neuroimaging in dementia
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Neuroimaging in dementia: an update for the general clinician

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Structural neuroimaging is a fundamental part of a routine dementia assessment to rule out treatable causes of cognitive impairment, and to support early, accurate dementia subtype diagnosis. Dr Rayment and colleagues discuss the different types of imaging and when they should be used, as well as analysing some typical imaging findings from common dementia subtypes.

This article is intended to provide an overview of the use of neuroimaging in the assessment of dementia for the non-specialist reader. We discuss the different imaging modalities, clinical and practical considerations regarding their use, and typical imaging findings in some of the more common dementia subtypes.

Types of imaging

Brain imaging techniques currently used in the UK for the clinical assessment of dementia are grouped into three categories: structural, functional and molecular.

Structural imaging includes computed tomography (CT) and magnetic resonance imaging (MRI). The images produced by these methods allow one to see the anatomical ‘structure’ of cerebral tissue. They are used to detect areas of visible brain atrophy or ischaemia.

Functional imaging includes $^{99m}$Tc-HMPAO single positron emission CT (HMPAO-SPECT), $^{18}$F-FDG positron emission tomography (FDG-PET) and the DaTscan, which use radioactive tracers to give an indication of the functioning of brain tissue. HMPAO-SPECT uses a lipophilic tracer that crosses the blood–brain barrier and moves into brain tissue by diffusion, the resulting SPECT image demonstrating the degree of cerebral blood perfusion. FDG-PET uses a glucose analogue to demonstrate the degree of cerebral glucose metabolism. In practice these two imaging modalities give similar information, and are used to identify impaired brain physiology prior to the onset of obvious atrophy. The DaTscan is a type of SPECT used specifically in the assessment of suspected Parkinson’s disease or dementia with Lewy bodies (DLB), and enables the visualisation of dopaminergic activity in the basal ganglia.

Finally, molecular imaging using radioactive traces that bind to specific molecules of interest is an emerging field. Amyloid-labelled PET scans, have been used in clinical trials to demonstrate the level of cerebral amyloid plaques in Alzheimer’s disease (AD). Two ligands, $^{18}$F-florbetapir and $^{18}$F-florbetaben, have recently been licensed for clinical use in the UK.

First-line imaging

A dementia assessment must include a clinical history, physical and cognitive examination, and screening blood tests – full blood count, urea and electrolytes, calcium, liver and thyroid function tests, glucose, vitamin B12 and folate. In addition, European Federation of Neurological Societies (EFNS) and National Institute for Health and Care Excellence (NICE) guidelines recommend the use of at least one structural image of the brain as part of the diagnostic process in dementia.1,2 The traditional reason for this is to rule out treatable causes of progressive cognitive impairment such as hydrocephalus, tumours and chronic haemorrhage (see Box 1), as it is not possible to do this reliably with clinical history and examination alone.3 With advances in imaging technology and improved

Box 1. Imaging can be used to rule out treatable causes of progressive cognitive impairment

Axial MRI (T2): Grossly enlarged ventricles in normal pressure hydrocephalus. Case courtesy of Dr G Balachandran, Radiopaedia.org, rID: 15942

Axial CT: Chronic left subdural haemorrhage. Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6136

Axial MRI (FLAIR): Large left frontotemporal meningioma. Case courtesy of Dr Frank Gaillard, Radiopaedia.org, rID: 30745
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understanding of pathological features in dementia, structural scans are now being used to support a more specific diagnosis of the dementia subtype.

In most parts of the UK, the first-line imaging modality in routine dementia assessment is a CT scan. The cost of a CT scan of the brain is relatively low (£78 in 2014).4 It can be done with or without contrast (oral or parenteral). The scan itself takes around five minutes. The dose of radiation, 2 mSv, is equivalent to approximately 20 chest X-rays, or eight months of background radiation. Improvements in resolution have resulted in CT scans being accepted by NICE as an alternative to an MRI in the initial assessment process.2 However, in order to visualise the hippocampal atrophy that is characteristic of early AD, it is necessary to view coronal sections or ‘reformats’ (Box 2). These are not always done routinely by radiology departments without specialist expertise in dementia and it is useful to ask for these when requesting the scan.

MRI brain scans are more expensive (£138 in 2014),4 and usually less accessible. They are well tolerated but they do involve a longer period of around 20 minutes lying in a narrow tunnel on a flat surface, which can be problematic for agitated, arthralgic, claustrophobic or obese patients. They are generally safe as long as metal objects are not inside the magnetic field with the patient. They generate a higher resolution image of cortical structures than CT scans, enabling a more detailed assessment of atrophy (Box 2). They are also superior in demonstrating cerebral ischaemia, especially subcortical ischaemia, and in changes associated with conditions such as frontotemporal dementia (FTD), multiple sclerosis, Parkinson’s plus syndromes and prion diseases.5 Further, younger people with Alzheimer’s disease may have non-amnesic presentations and here MRI may be needed to localise atrophy to the more posterior regions of the pre-cuneus and posterior cingulate cortex.6 In this younger population, atypical and reversible causes of dementia are proportionally more likely than in the elderly. Consequently, there are substantial benefits in choosing MRI over CT in the first-line assessment of progressive cognitive impairment in this patient group.7 Because of this, in spite of the additional cost, NICE recommends MRI as the preferred first-line imaging modality.4 Also, because of the additional information that an MRI may provide, if a patient has a normal CT brain but clinically significant cognitive impairment, then it is a reasonable next step to order an MRI brain scan.

It could be argued that in cases of advanced dementia, neuroimaging may not be beneficial. This is for two reasons. Firstly, it can be difficult to distinguish the generalised atrophy of advanced dementia from age-related brain volume loss in very elderly patients. Secondly, the treatable causes of dementia typically involve neurosurgical or radiological interventions. If the patient would not be suitable for such procedures then carrying out a brain scan may not alter the management plan for the patient.

Typical imaging findings in dementia subtypes

In a typical case of Alzheimer’s disease, the early clinical presentation is one of difficulty with recall of recent information, and language problems. The imaging finding is one of atrophy in the medial temporal (Box 2) and parietal lobes.

The ‘stepwise’ decline of the multi-infarct subtype of vascular dementia (VaD), caused by repeated large vessel cortical strokes, is the most commonly taught subtype. However, the most common subtype of vascular dementia seen in memory clinics is one
of subcortical VaD (Box 3, a) in which patients develop progressive impairment due to deep white matter changes over a number of years. Subcortical VaD tends to present clinically with slowness of thinking, difficulty with complex tasks, early gait disturbance and early incontinence.

FTD presents in its behavioural subtype with progressive disinhibition, changes in personality and decline in interpersonal skills. The imaging finding is one of cerebral atrophy more pronounced in frontotemporal regions (Box 3, b).

Dementia with Lewy bodies (DLB) can present with fluctuating cognition, visual hallucinations, parkinsonian symptoms and rapid eye movement (REM) sleep behavioural disorder. The findings on structural scans may be subtle and non-specific (Box 3, c). Therefore, the condition is often diagnosed clinically with structural imaging used to rule out other diseases, and functional imaging being used where necessary.

**When to request functional imaging in the assessment of dementia**

The best evidence for the use of HMPAO-SPECT and FDG-PET is in differentiating AD from FTD, which can be difficult based only on clinical and structural scan findings (Box 4). NICE guidelines recommend that functional neuroimaging with HMPAO-SPECT or FDG-PET should be considered to help differentiate between non-dementia, AD, VaD and FTD if the diagnosis is in doubt. EFNS dementia guidelines state that FDG-PET is particularly useful in differentiating AD from FTD with more than 95% specificity in young-onset dementia. HMPAO-SPECT has been more widely accessible to date, but is gradually being replaced by FDG-PET, which gives a better spatial resolution, the ability to quantify changes, and can demonstrate a higher degree of hypometabolism. Further, PET scans nowadays incorporate a diagnostic CT allowing structural co-relation of the functional changes. A recent comparison demonstrated that FDG-PET had superior sensitivity and specificity than HMPAO-SPECT in the diagnosis of dementia.

Both HMPAO-SPECT and FDG-PET involve the administration of an intravenous tracer, a waiting period prior to the scan, and lying still on a flat surface. The level of radioactivity received is similar in both tests and comparable to CT scans. The cost of a HMPAO-SPECT brain in one hospital was £514 in 2012, with FDG-PET scans costing up to £1500. However, these costs are rapidly reducing as the ligands are now off patent.

The dopaminergic SPECT DaTscan (Box 5) involves the same procedure as the HMPAO-SPECT but involves a ligand which binds to dopamine transporters in the synapses of the nigrostriatal pathway. A significant reduction in dopaminergic activity in this region is indicative of diseases such as idiopathic Parkinson’s, Parkinson’s plus syndromes and dementia with Lewy bodies (DLB). NICE recommends that functional neuroimaging with DaTscan should be used to help establish diagnosis in those with suspected DLB if the diagnosis is in doubt. EFNS dementia guidelines attribute around 85% sensitivity and specificity to DaTscans for differentiating AD from DLB. This is clinically important not least because the management of psychotic symptoms in DLB differs from management of the same symptoms in AD as DLB patients are extremely sensitive to antipsychotic medication. DaTscan can also be
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useful to differentiate between patients with idiopathic Parkinson’s disease and neuroleptic-induced parkinsonism, as the latter should have a normal dopaminergic scan.

Molecular imaging
Amyloid imaging is a new type of PET scan, this time using ligands that bind to amyloid in cerebral tissue. Amyloid plaques have been associated with AD since the first histological studies and these plaques are considered to be the first step in the pathophysiology of the disease. Amyloid PET scanning with the Pittsburgh B compound (PiB) has been used over the last few years to detect significant cortical amyloid plaques as inclusion/exclusion criteria and secondary outcome measures for trials of anti-amyloid treatments in AD (Box 6).

Box 5. DaTscan can be used to help establish diagnosis in those with suspected DLB if the diagnosis is in doubt

Axial dopaminergic SPECT of a normal brain

Axial dopaminergic SPECT of a brain demonstrating changes associated with Parkinson’s disease (reduced uptake in the putamen)

Box 6. Amyloid PET scanning with the Pittsburgh B compound to support early, specific dementia subtype diagnosis. MRI may provide additional information to a CT scan and is useful as a second line, or as a first line particularly in atypical or young-onset cases of cognitive impairment. Functional imaging is useful as a second- or third-line investigation where the dementia diagnosis is in doubt, and for differentiating FTD from AD. Recent evidence suggests FDG PET is more sensitive and specific than HMPAO-SPECT. DaTscan is a type of SPECT used to differentiate DLB from other illnesses. Amyloid molecular imaging is currently used in research settings to identify plaques associated with Alzheimer’s disease but to date has a limited role in clinical assessment.

Research is underway to develop molecular imaging based on radioactive tracers that bind to tau proteins and even products of neuroinflammation, both of which are seen in the pathophysiology of AD.

Summary
In summary, structural neuroimaging is an important part of a routine dementia assessment to rule out treatable causes of cognitive impairment, and

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Declaration of interests
Dr Kuruvilla has received speaker fees from GE Healthcare and Eli Lilly & Co.
References

News

Guanfacine for ADHD

Guanfacine (Intuniv) prolonged-release tablets are now available in the UK for the treatment of attention deficit hyperactivity disorder (ADHD) in children.

Guanfacine is a new once-daily non-stimulant designed for children aged 6–17 years for whom stimulants are unsuitable, not tolerated or have been shown to be ineffective.'

The availability of this new non-stimulant may represent an important alternative treatment option, enabling physicians to tailor ADHD therapy to those patients for whom stimulants are not suitable, said Dr Chris Steer, Consultant Paediatrician, NHS Fife.

The drug is a selective alpha2A adrenergic receptor agonist and should be used as part of a comprehensive ADHD treatment programme.

Studies (Hervas A, et al. Eur Neuropsychopharmacol 2014; 24:1861–72) have shown the drug to improve the symptoms of ADHD compared with placebo. The most common adverse reactions reported included somnolence, headache, fatigue, upper abdominal pain and sedation.

MS campaign advocates regular contact with specialists

A new campaign has been launched to target people with multiple sclerosis (MS) who are missing out on vital MS services.

The IMSg campaign (supported by Biogen) aims to highlight the benefits of regular engagement with MS specialists in order to ensure people are making informed decisions about their disease management based on the latest information and research. The IMSg campaign includes a website www.ims-co.uk giving people living with MS and those affected by the condition access to information and advice from MS specialists.

‘Litany of failures’ revealed in dementia report

A report into the standard of care received by dementia patients in NHS hospitals has revealed a ‘litany of failures’, according to the Alzheimer’s Society.

The information contained in the report was gathered from a total of 68 NHS Trusts. The multitude of problems ranged from unchanged soiled sheets and a lack of personalised care to being treated with excessive force.

The report, Fix Dementia Care (www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2907) reveals that approximately 4926 people with dementia are discharged at night, between 11pm and 6am.

The report says in the three worst performing hospitals, four to five people were being discharged overnight each week.

In one trust, 702 people with dementia fell in 2014–15, the equivalent of two falls a day. Last year, 28% of people over the age of 65 years who fell in hospital had dementia. Independent analysis has shown that on average, if a person with dementia falls in hospital, the duration of their time in hospital is almost four times as long.