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GUEST EDITORIAL

# Clinical use of neuroimaging in dementia: an international perspective

Increasingly, a large number of neuroimaging techniques are being developed and used for research, with some ultimately entering clinical practice (Scheltens *et al.*, 2002; O'Brien, 2007). For most clinicians working with dementia patients, it can be very hard to keep abreast of developments in the field. For example, when does a potentially exciting new technique for diagnosis or monitoring disease progression become sufficiently validated to be accepted by the scientific community? When does such a validated method for research then become justified for use in routine clinical practice? Closely linked to this, when does one have sufficient evidence that a diagnostic tool changes practice to engage with discussions with those commissioning or paying for health services to make a strong business case for funding for the method to be made available? It is also often far from clear, when faced with a patient with cognitive difficulties, exactly what scan should be requested, at what point and why. If one scan is uninformative or equivocal then what should be the next steps? Are there factors that limit sensitivity of a given technique, such as age? Is it worth suggesting another form of brain imaging to find further information, should one wait and monitor the patient clinically over time, or even repeat the same scan to look at progression? These are challenging but important questions which are all addressed in this supplement. Different papers look critically at what imaging methods are currently available – or may very soon become available – in the clinic, what they can show in particular circumstances, how they should be interpreted and how and when such scans should be requested.

This supplement brings together internationally recognized experts in the imaging field to address these key issues. Marco Pasi, Anna Poggesi and Leonardo Pantoni describe the use of computed tomography (CT) scanning in dementia. CT is undoubtedly the most common imaging method worldwide that is applied to people with dementia but, as we see in later papers, it is by no means certain that every person with suspected dementia undergoes a CT scan, even in highly developed healthcare systems. CT is good at detecting space occupying lesions and can help in most cases of suspected vascular dementia in determining whether significant cortical or subcortical vascular change is present. Regional atrophy can also be assessed and new multislice scanners can allow, following coronal reconstruction, accurate visualization of the medial temporal lobe in a manner that was hitherto impossible. CT is a robust method, is widely available and is the cheapest imaging method. While it is less sensitive and specific than magnetic resonance imaging (MRI), it still has a pivotal place in the assessment of those presenting with cognitive impairment and will continue to do so for the foreseeable future.

Mike Wattjes discusses the role of MRI. Like CT, MRI is helpful in identifying potentially treatable causes of dementia but can, to a greater extent than CT, also support clinical diagnosis in a memory clinic setting by identifying certain patterns of atrophy and vascular damage with greater accuracy than CT. In addition, MR can detect certain aspects of pathology not accessible by CT – for example, cerebral microbleeds which are related to cerebral amyloid angiopathy. It can also show changes in other dementias. Those not familiar with the "hot cross bun" sign or the "putamenal ring" sign will be better informed after reading Mike Wattjes' paper.

Karl Herholz describes the use of perfusion single photon emission computed tomography (SPECT) and $^{18}$F-2-fluoro-D-deoxyglucose (fludeoxyglucose)-positron emission tomography (FDG-PET) imaging. Whilst they are different methods, with perfusion SPECT being related to blood flow and FDG PET assessing metabolism, both show similar changes in degenerative dementias. PET imaging may be more sensitive and specific than CT, though there have been few direct comparisons. Studies demonstrate temperoparietal hypoperfusion and hypometabolism in Alzheimer's disease (AD), frontal hypoperfusion and hypometabolism in frontotemporal dementias (FTD) and more posterior parietal and occipital hypoperfusion in dementia with Lewy bodies (DLB). Such signs can be helpful diagnostically, but most sets of guidelines advocate the use of SPECT and PET only for cases where diagnostic doubt remains following clinical assessment and structural imaging. The very important diagnostic reason for this is the "added value" that imaging gains over a baseline assessment, given that imaging

markers are usually in the region of 75% to 85% accurate rather than near 100%. If cases at very high likelihood of having a certain diagnosis, or indeed very low likelihood, are sent for diagnostic imaging then the added value of the additional imaging is very small. This is because a positive scan in someone who is very unlikely to have the disorder is much more likely to be a false positive than really indicate a person has dementia. Similarly, if someone is very likely to have dementia following baseline assessment a negative scan in that person is far more likely to reflect a false negative than really indicating the person does not have dementia. As such, the diagnostic gain from people with high and low certainty of having dementia is limited (Scheltens *et al.*, 2002). However, there is maximum gain when diagnostic uncertainty exists, and for this reason guidelines have generally advocated the use of methods like SPECT and PET imaging for those where there is diagnostic doubt.

Zuzana Walker discusses the use of FP-CIT (dopaminergic) SPECT imaging in the assessment and diagnosis of DLB. She highlights that there are many different ways of visualizing integrity of the dopaminergic system using a variety of SPECT and PET ligands, but that ligands for the dopamine transporter have proved most helpful for identifying the nigrostriatal degeneration associated with both Parkinson's disease and DLB. Arguably, FP-CIT imaging is the method that has been subject to the best validation for dementia through a large multicenter study and this has shown good diagnostic accuracy for distinguishing between DLB and AD (McKeith *et al.*, 2007), though it will not reliably distinguish DLB from other parkinsonian dementias like progressive supranuclear palsy, corticobasal degeneration and multisystem atrophy. There may also be abnormalities in frontotemporal dementia if there is concurrent parkinsonism, though this remains to be examined further.

Victor Villemagne and Chris Rowe discuss the exciting development of amyloid imaging. As with dopaminergic imaging, there are several amyloid imaging compounds currently in development and three key ones in clinical trials. Amyloid imaging has shown that it can distinguish between people with AD and FTD and younger controls, that many subjects with mild cognitive impairment have increased amyloid binding, and that a substantial proportion of apparently healthy normal older people also have increased amyloid (this proportion rises with possession of ApoE4 allele and with higher age). Amyloid imaging may be more sensitive than FDG PET for diagnosis of AD, but specificity may be an issue, not only because of the high rates in normal aging but because increased binding is found in DLB. Increasingly though, this highlights the need to target imaging depending on the clinical questions being asked. For example, if the question is "does the person suffer from AD or DLB?", then a dopaminergic scan would be the scan of choice. If the question is "does the person suffer from AD or FTD?", then a perfusion/glucose scan or amyloid scan would be more appropriate. If the question is "can we identify people with high levels of cortical amyloid in vivo?", then amyloid imaging would be the investigation of choice. Since amyloid levels appear to rise early and remain relatively stable over time, detecting disease progression may be better undertaken by other methods such as serial structure MR or serial glucose PET, unless the question is of amyloid removal in which case serial amyloid imaging may be the preferred method.

It should be remembered that imaging represents one component of current work on biomarkers; there has been considerable progress in cerebrospinal fluid (CSF) markers for AD and other dementias, and indeed these markers do show a correlation with certain imaging features, especially between decreased CSF amyloid and increased amyloid binding on PET, and betwen atrophy on MR and raised CSF tau and phospho-tau. Klaus Ebmeier discusses other MRI methods including functional MR, MR spectroscopy, and diffusion tensor imaging. All have already made important contributions to understanding neurobiology and correlations with symptoms in dementia; whilst some have been advocated diagnostically, it still remains unclear which of these methods will ultimately prove to be both valid and accurate enough for routine clinical use in relation to dementia. The final paper is by Craig Ritchie and colleagues who discuss the extent to which current imaging changes are esoteric activities very much limited to specialist research centers, and how much they are, or should be, more widely disseminated for routine clinical care. The specific examples of the practical use of imaging are provided for countries in different continents including Scotland, Argentina, the USA, France, the Czech Republic and Australia. The conclusion is that clinically applicable imaging methods are currently available, with high diagnostic utility, but for many methods further work in terms of wider validation needs to be undertaken before they can be widely recommended.

Overall, therefore, there is emerging consensus that imaging changes are not only useful but increasingly essential in the assessment and diagnosis of those with dementia. Imaging features are now becoming incorporated in diagnostic criteria, good examples of which are the need

for cerebrovascular disease on imaging to fulfil criteria for probable vascular dementia (Román *et al.*, 1993), the requirement for dopaminergic abnormalities in the basal ganglia as a suggestive feature for probable DLB (McKeith *et al.*, 2005), and the incorporation of MR, SPECT and PET changes in proposed new diagnostic criteria for early AD (Dubois *et al.*, 2007) and proposed new NINDS diagnostic criteria for AD, mild cognitive impairment due to AD and so called pre-clinical AD. In addition, there is emerging consensus from different guideline groups on when imaging should be undertaken. It is generally accepted that structural imaging should be used to exclude treatable causes of dementia and that other imaging investigations may be useful when there is diagnostic doubt. The guidelines from the European Federation of Neurological Sciences for the diagnosis and management of AD were recently published (Hort *et al.*, 2010) and their recommendations regarding imaging are as follows:

- CT and MRI may be used to exclude treatable causes of dementia.
- Multislice CT and coronal MRI may be used to assess hippocampal atrophy to support a clinical diagnosis of AD (Level B).
- FDG PET and perfusion SPECT are useful adjuncts when diagnosis remains in doubt (Level B).
- Dopaminergic SPECT is useful to differentiate AD from DLB (Level A).
- Follow-up with serial MRI is useful in a clinical setting to document disease progression (Good Practice Point).

Other issues are of course also important. Interpretation of scans can vary considerably depending on who actually reports the images, the questions that they are asked on the request form and the experience and skill of the person interpreting the report. Operator independent unbiased methods, whether voxel based or involving neural networks or support vector machines, may offer advantages in the future, especially for less experienced raters. At the clinical level, bringing together clinicians, radiologists and nuclear medicine specialists for regular clinico-radiological meetings is to be strongly recommended and can almost be regarded as a condition sine qua non in clinics seeing these patients. It can resolve key clinical and management issues and foster closer relationships and understanding between professionals, allow for more appropriate use of imaging, better quality reporting, and also act as a focus for continued professional development, audit, teaching and research, and precludes the biggest danger of all – judging the image (whatever its modality) out of the clinical context.

Overall, this is a very exciting time in the journey of establishing firmly the place of imaging in the diagnosis and assessment of people with dementia. It certainly has a more central role than it did a decade ago, and this direction of travel seems set for the future.

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