Neuroimaging

Diagnosis of dementia is becoming easier with the emergence of neuroimaging, which is now used as the leading ancillary investigation. Its traditional purpose was to rule out potentially treatable causes for cognitive impairment, e.g. tumours, haematomas, lesions and hydrocephalus, and advances in technology mean that it is now also used to support diagnosis of the type of dementia. However, it could be argued that in cases of advanced dementia, neuroimaging may not be beneficial because it can be difficult to distinguish the generalised atrophy of advanced dementia, from age-related brain volume loss in very elderly patients. Most clinical guidelines now recommend at least one structural imaging procedure in every patient where dementia is suspected. The role of imaging in dementia is to exclude "treatable" causes, to clarify diagnostic dilemmas, and to identify early onset cases for possible innovative therapies in clinical trials.

The role of neuroimaging in the assessment of dementia:-

- Neuroimaging is an important component of the clinical assessment of dementia.
- Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are used to look at brain structure.
- Single Photon Emission Computed Tomography (SPECT) and Positron Computed Tomography (PET) scans are used to look at brain function.
- Neuroimaging can be used to assist in diagnosis and in clinical drug trials.

Treatable structural causes of dementia can be excluded:-

- Structural brain lesions can cause dementia syndromes.
- These include tumours, haemorrhages, CJD, prion disease and hydrocephalus.
- These conditions are potentially reversible.
- Either CT or MRI can be used to identify these conditions.

Alzheimer's disease (AD):-

- The first presenting feature in Alzheimer's disease is usually episodic memory loss.
- This is mirrored by focal atrophy in the medial temporal lobe and can best be seen in coronal sections on MRI.
- CT can also be used but it is non-specific and is harder to interpret for a non-specialist.
- Structural imaging can also identify other Alzheimer's syndromes with focal atrophy.
- The progression of mild cognitive impairment to Alzheimer's disease dementia can be predicted to some extent by structural and functional imaging biomarkers

Types of imaging

Brain imaging techniques currently used 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 lack of blood supply. The cost of a CT scan of the brain is relatively low and takes around five minutes.

The dose of radiation is equivalent to approximately 20 chest X-rays, or eight months of background radiation. MRI brain scans are more expensive and are tolerated well but they do involve a longer period of around 20 minutes lying in a narrow tunnel on a flat surface. This can be problematic for agitated, arthritic, claustrophobic or obese patients. They generate a higher resolution image of cortical structures than CT scans, enabling a more detailed assessment of degeneration. They are also superior in demonstrating cerebral blood supply restrictions, and in changes associated with conditions such as frontotemporal dementia (FTD), multiple sclerosis, Parkinson's plus syndromes and prion diseases.

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 degeneration in the medial temporal and parietal lobes.

The 'stepwise' decline of the multi-infarct subtype of vascular dementia (VAD), caused by repeated large strokes in the outer layers of the brain, is a common subtype. However, the most common subtype of vascular dementia seen in memory clinics is one of subcortical VAD 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 degeneration more pronounced in frontal temporal regions. 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 Therefore, the condition is often diagnosed clinically with structural imaging used to rule out other diseases, and functional imaging being used where necessary.

Functional imaging reveals how well cells in various brain regions are working by showing how actively the cells use sugar or oxygen. Functional imaging includes single positron emission CT (SPECT), F-FDG positron emission tomography (FDG-PET) and the DATscan, which use radioactive tracers to give an indication of the functioning of brain tissue. SPECT uses a tracer that crosses the blood-brain barrier and moves into brain tissue by diffusion, the resulting SPECT image demonstrating the degree of cerebral blood flow. 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.

For example, studies with fluorodeoxyglucose (FDG)-PET indicate that Alzheimer's disease is often associated with reduced use of glucose (sugar) in brain areas important in memory, learning and problem solving. (Fluorodeoxyglucose is a short-lived radioactive form of sugar injected into people during PET scans to show activity levels in different parts of the brain). However, as with the shrinkage detected by structural imaging, there is not yet enough information to translate these general patterns of reduced activity into diagnostic information about individuals. In Alzheimer's, low activity is mostly in the back part of the brain; in FTD, low activity is mostly in the front of the brain.

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 dopamine (a neurotransmitter) related activity in the brain.

The best evidence for the use of SPECT and FDG-PET is in differentiating Alzheimer’s from FTD which can be difficult based only on clinical and structural scan findings. DATscan involves the same procedure as SPECT but involves a ligand which binds to dopamine transporters. 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). (*Ligand* is a substance that forms a complex with a biomolecule to serve a biological purpose. In protein-*ligand* binding, the *ligand* is usually a molecule which produces a signal by binding to a site on a target protein)

M**olecular** imaging uses radioactive tracers that bind to specific molecules of interest. It 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.
Amyloid plaques have been associated with Alzheimer’s since the first histological studies and these plaques are considered to be the first step in the pathophysiology of the disease. Amyloid PET scanning 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 Alzheimer's. Given the high cost of this novel imaging technique it is only in highly specific cases following expert opinion where the confirmed presence of amyloid would possibly alter the management of the case.

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 Alzheimer's.

Positron emission tomography (PET) is used for both functional and molecular imaging studies of the brain. There are a few types of scan that can be used in the diagnosis of dementia. FDG PET scans show glucose metabolism which can indicate the brain isn't functioning properly. Amyloid PET scans reveal the level of amyloid, one of the key hallmarks of Alzheimer's disease, in the brain. *More recently a new tau PET tracer shows low uptake in control subjects, intermediate uptake in mild cognitive impairment, and intense tau pathology spreading across the frontal and temporal cortex in Alzheimer's disease.*