Neuroimaging in Dementia

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Dementia: Clinical Background

Dementia is usually defined as an acquired condition involving multiple cognitive impairments that are sufficient to interfere with activities of daily living. It is usually but not necessarily progressive. Memory impairment is one of the most common deficits, but other domains such as language, praxis, visual-perceptive and most notably executive functions are often involved. With increasing loss of function due to these cognitive problems, there is progressive difficulty with activities of daily living. Many of the diseases that cause dementia have a relentlessly progressive course with an insidious onset; many have long durations (e.g. 5–10 years from diagnosis) and relatively prolonged end-stage period of where all self-care and independence is lost. Dementia places tremendous burdens on patients, their families and carers and on health and social care systems. The most important causes of dementia have an age-related incidence. As a result the prevalence and societal costs of dementia are predicted to rise dramatically over the coming decades.

In 2000, prevalence data of 11 European population-based studies were pooled to obtain stable estimates of prevalence of dementia in the elderly (>65 years). Age-standardized prevalence was 6.4 % for dementia (all causes), 4.4 % for Alzheimer's disease (AD) and 1.6 % for vascular dementia (VaD). Prevalence of dementia was higher in women than in men and nearly doubled with every 5 years increase of age: from 0.8 % in the group age 65–69 years to 28.5 % over the age of 90 years.

Need for a Nosological Approach

Dementia is a syndrome, not a disease, and has many and varied causes. The diagnostic workup is meant to identify the underlying cause with a particular emphasis on picking up treatable conditions. Diagnosis is critically dependent on careful history taking from patient and informant followed by clinical and cognitive examination supported by ancillary investigations, of which neuroimaging is one of the most important. The a priori chance of a particular disease being present is dependent on age. The younger the patient, the greater the chance that one of a wide range of underlying pathologies is the cause of the cognitive problems. Diseases like frontotemporal lobe degeneration (FTLD) and Huntington's disease (HD) tend to occur more often before the age of 70; genetic forms of AD almost exclusively occur at young ages and rare metabolic causes are more likely in early adulthood (see Table 1). In the older patient AD, Lewy body dementia (LBD) and vascular disease are by far the most common pathologies; mixed disease is very common: notably AD with vascular disease has been shown to be the most prevalent in post-mortem series of older individuals (>85 years).

The nosological approach is facilitated by the use of clinical criteria. In the table below, the main disease categories and their published clinical criteria are listed with the use of imaging highlighted. From the table, it may be inferred that for the majority of diseases, no specific imaging criteria have been formulated; however, it is also notable that more recent revisions of criteria are increasingly including imaging (for positive as well as negative predictive value).

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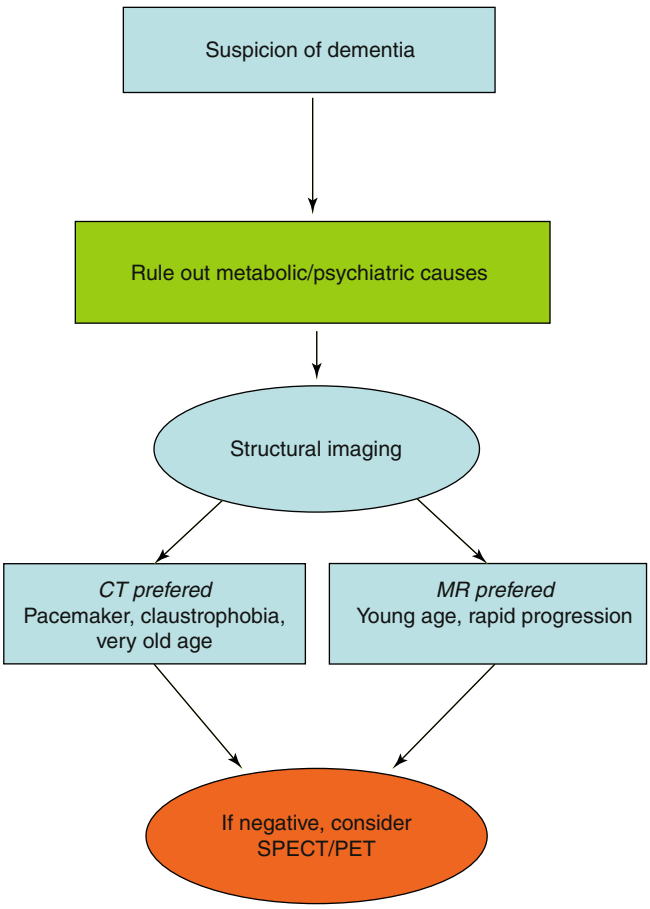
Table 1 Differential diagnosis in young-onset dementia

Disease	MRI findings	Clinical clues	Additional tests
Alzheimer's disease	Posterior cingulate atrophy, medial temporal atrophy	Family history, visuospatial and apraxia > memory	CSF (abeta and tau); FDG-PET; amyloid PET
Frontotemporal lobe degeneration	Frontotemporal atrophy Temporal atrophy (asymmetrical or symmetrical)	Family history, language, behaviour	FDG-PET
Corticobasal degeneration	Frontoparietal atrophy; may be asymmetrical	Asymmetrical parkinsonism, dyspraxia and myoclonus; alien limb	CSF; dopamine imaging
Small vessel disease	Strategic infarcts, lacunes, WMH, microbleeds, microinfarcts, dilated VRS	TIA; stroke	Vascular risk factors
Vasculitis	WMH, patchy enhancement, multifocal diffusion restriction	TIA, multifocal	ESR and CRP elevation; CSF, DSA, serology
Multiple sclerosis	Disseminated WM lesions, black holes Gad enhancement	Relapses; other neurological findings	CSF oligoclonal bands
Creutzfeldt-Jakob disease	Abnormal DWI basal ganglia or neocortex	Myoclonus; cerebellar ataxia	EEG, CSF tau and 14-3-3 protein
Paraneoplastic or limbic encephalitis	Temporal lobe lesions; thalamic swelling	Subacute onset; other neurological findings	CSF antibodies
Infectious	WM lesions, enhancement	Fever, HIV, lues	Serology, CSF, culture
Metabolic	WM lesions, GM lesions, lactate in spectroscopy, diffusion restriction	Stroke-like episode	CSF, serology, muscle biopsy, genetics

Modified from Ridha B, Josephs KA. *Neurologist*. 2006;12:2–13

The Toolbox



When structural imaging is equivocal or does not lead to the diagnosis, functional imaging may add diagnostic value. Second-line neuroimaging investigation includes metabolic information obtained by using SPECT or PET or physiological information obtained by using diffusion or perfusion MRI. For example, in the early stages of FTLD, there may not exist any discernible atrophy. FDG-PET or HMPAO-SPECT might demonstrate decreased metabolism or hypoperfusion preceding tissue loss on structural imaging. In the future, molecular imaging may provide even more disease-specific information. PET tracers binding to amyloid are a good example of such developments, although their role in the diagnostic algorithm still remains to be established.

Standard Structural MR Imaging Protocol

The prevalence of AD and vascular pathology means that suggested first aims in the imaging evaluation of a patient suspected of having dementia – beyond exclusion of a surgically treatable disorder – are:

(I) To assess the extent and pattern of brain atrophy, in particular medial temporal lobe atrophy (for evidence of Alzheimer's pathology)
(II) To determine the degree of vascular damage, including the occurrence of strategic vascular lesions

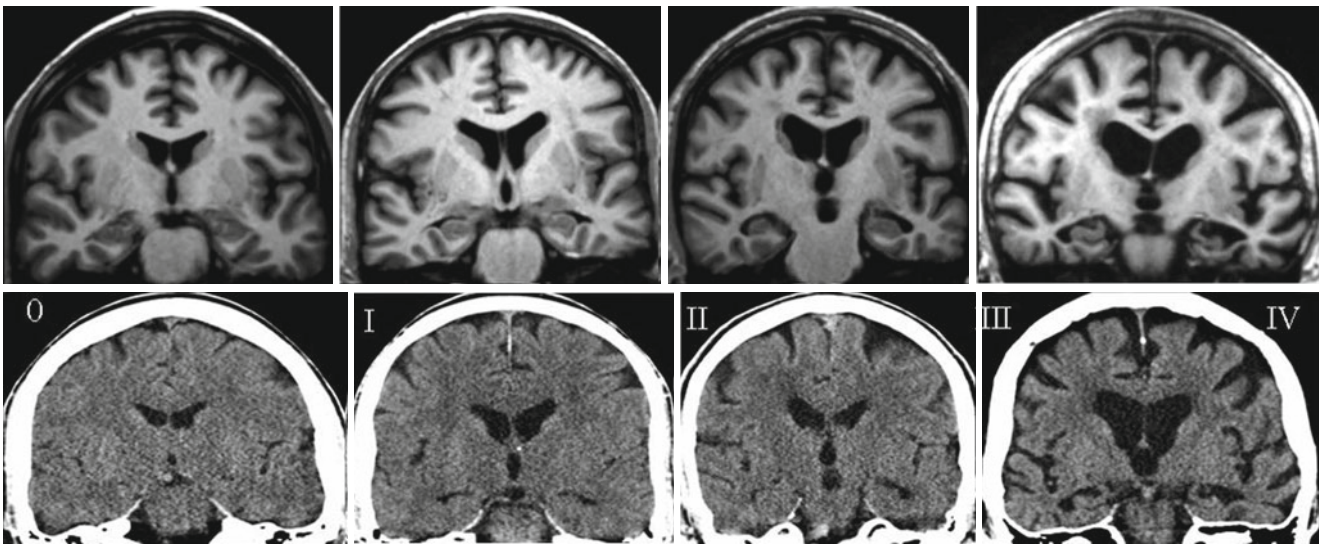
Standard Structural MRI Protocol: No Routine Contrast Administration

- Sagittal 3D T1-weighted gradient echo with 1 mm isotropic voxels
  - Coronal reformats (MPR) perpendicular to long axis of hippocampus
  - Detection of regional atrophy patterns (e.g. hippocampal)
- Transverse FLAIR with 3–5 mm slices (can be MPR form 3D-FLAIR)
  - Detection of ischemic white matter lesions and lacunes
- Transverse T2-weighted TSE/FSE with 3–5 mm slices
  - Detection of thalamic lesions and vessel patency
- Transverse T2* gradient echo with 3–5 mm slices
  - Detection of microbleeds
- Transverse DWI/ADC
  - Detection of recent infarcts and CJD

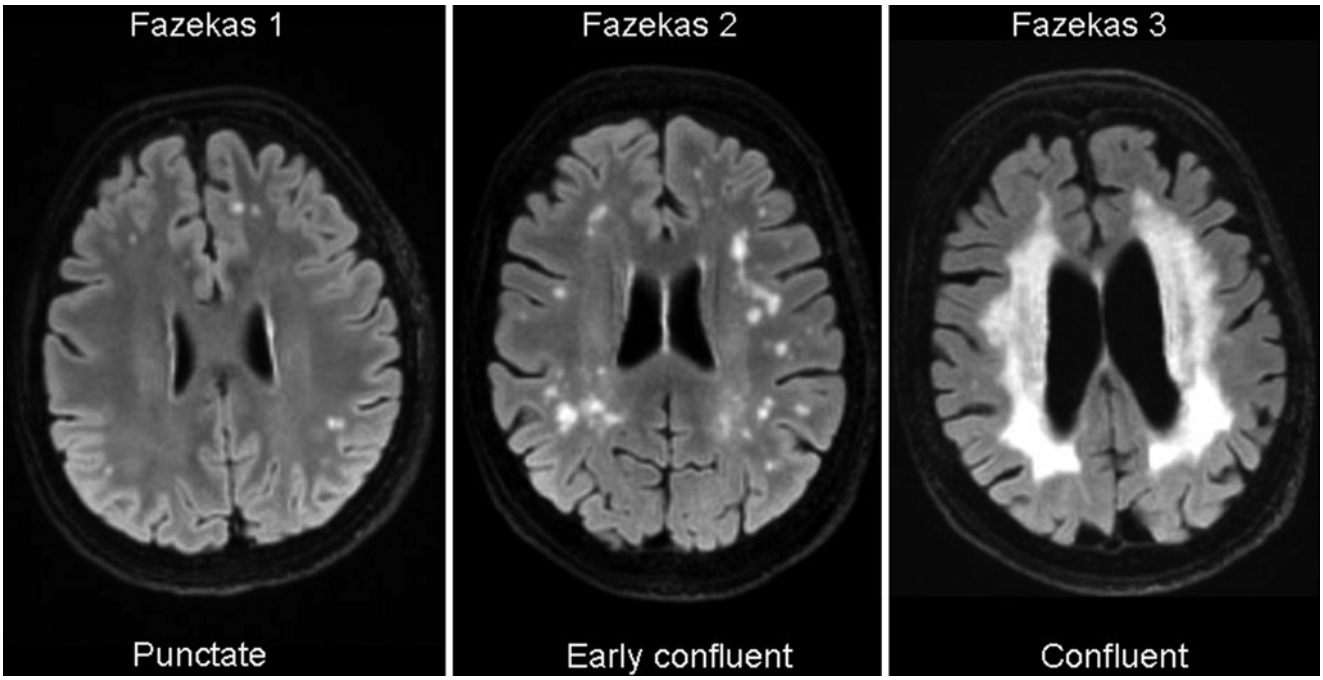
Table 2 Visual assessment of medial temporal lobe atrophy (MTA)

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampus
0	N	N	N
1	↑	N	N
2	↑↑	↑	↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

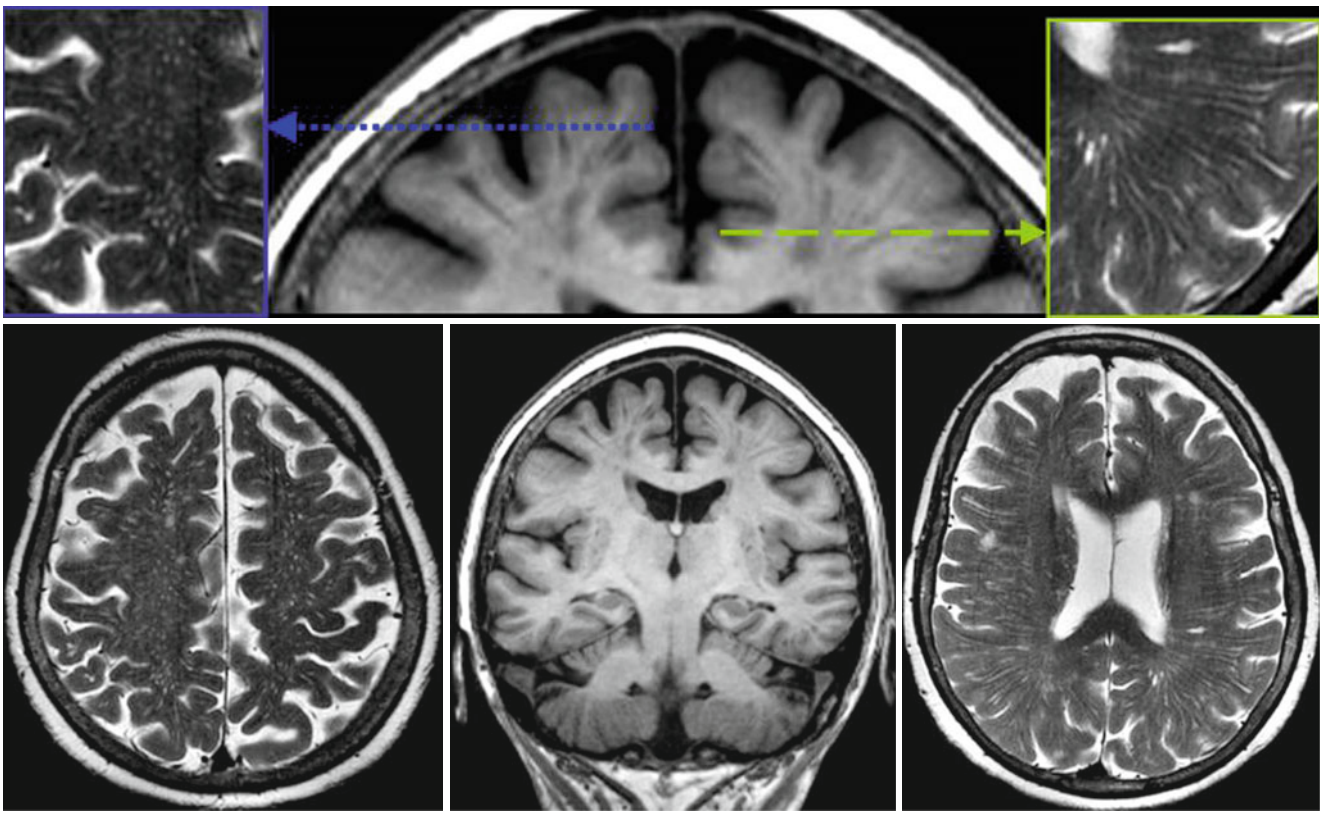
According to Scheltens et al.
(↑ increase, ↓ decrease, *N* normal)



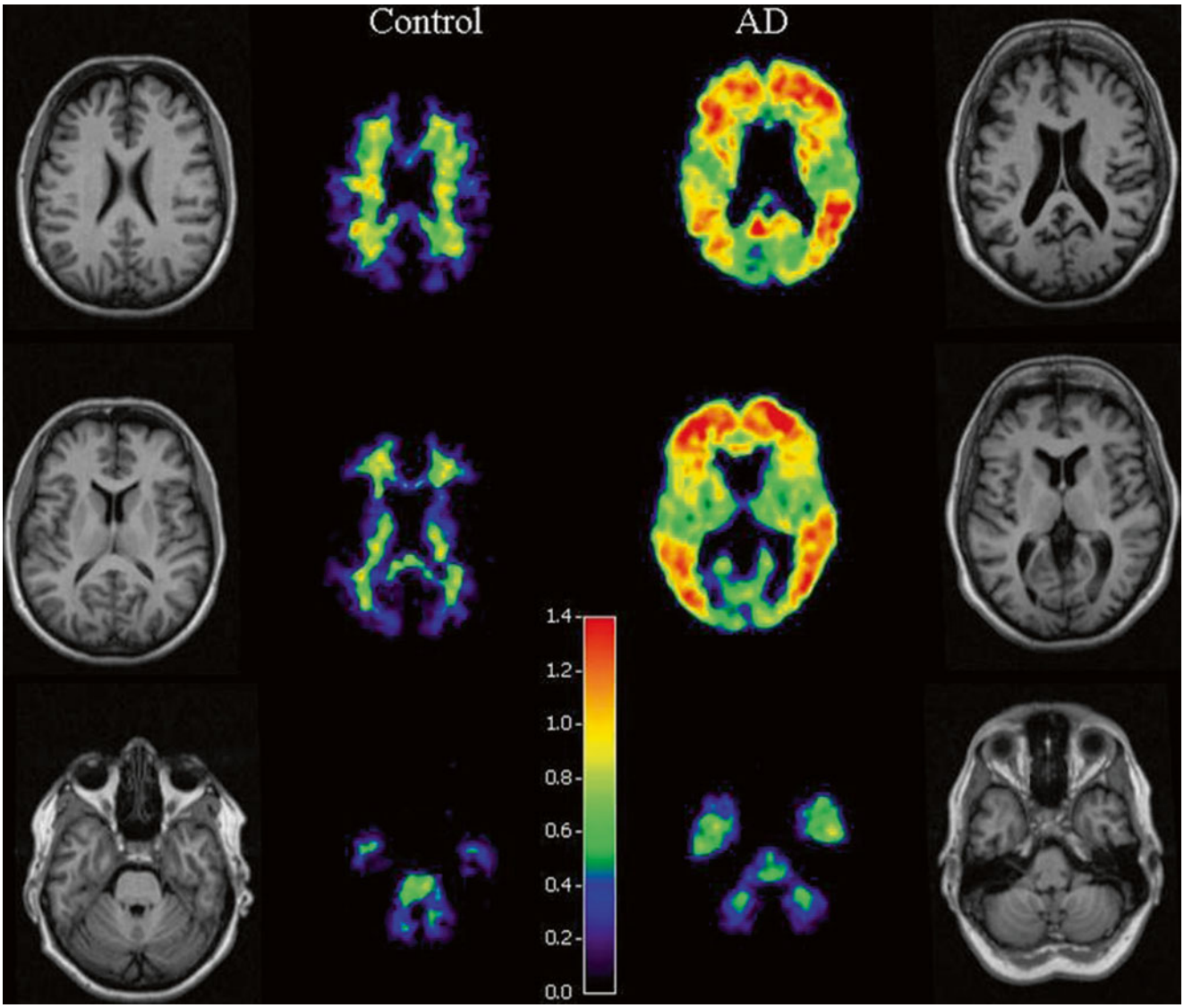
Visual rating of MTA. In these same-day scans, a perfect similarity between MRI and CT is noted for assessment of the medial temporal lobe for visual rating of MTA (Modified with permission from *Radiology*. 2009;253:174–83)



WMH scoring using Fazekas' rating scale



Virchow-Robin spaces (VRS). This 71-year-old woman presented with subjective memory complaints only. The coronal T1-weighted image in the middle show normal hippocampi and ventricles. There is diffuse widening of the VRS which are seen as sharply demarcated structures with signal intensity close to CSF. Note that their appearance on axial T2-weighted images depends on their orientation relative to the imaging plane, leading to a dot-like appearance when cut cross-sectionally (*left*) or stripe-like when cut tangentially (*right*)



Amyloid PET in AD. The binding potential of the tracer ^{11}C-Pittsburgh compound-B (PIB) is low in healthy controls and confined to the white matter. By contrast, abnormal uptake occurs in the cortex of AD patients, probably many years before the diagnosis due to abnormal amyloid deposition.

Normal Ageing

Age-related abnormalities do not occur in all elderly persons. Some elderly individuals have a perfectly normal brain that is indistinguishable from that of a young person. This observation is in line with the concept of subdividing human ageing in *successful ageing* and *usual ageing*. Successful ageing is defined as minimal physiologic loss, even when compared with younger individuals, and usual ageing as the presence of disturbance of physiologic functions (such as systolic hypertension, abnormal glucose tolerance test) without overt neurologic symptoms. Elderly individuals with a normal appearance of the brain on imaging might be representatives of the group of successful ageing human beings. Age-related changes that are apparent on radiological examinations do not always have functional consequences. An impressive load of brain lesions may be an incidental finding in an elderly individual, who has no neurological or intellectual complaints whatsoever and who, apparently, is capable of having a normal, independent life.

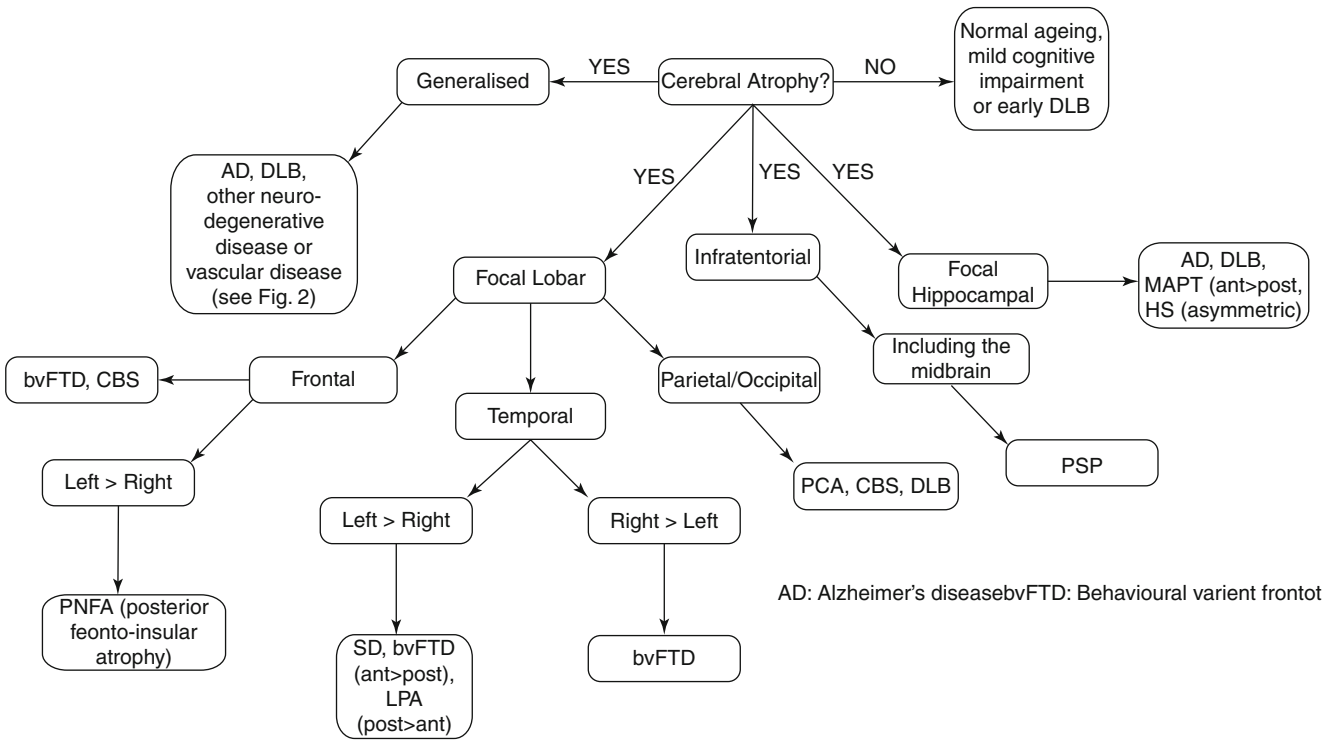
Normal ageing and neurodegenerative disorders may be difficult to distinguish. One reason is the similarity of the abnormalities that are associated with these conditions. In several neurodegenerative disorders, the abnormalities only differ in pattern from those occurring in normal ageing. In other neurodegenerative disorders, the abnormalities really are similar, also in pattern, and the amount of abnormalities in relation to a patient's age is the only factor that permits

distinction from normal ageing. Another phenomenon that complicates distinguishing normal ageing from other neurodegenerative disorders is the fact that due to the high prevalence of the latter, these conditions often coexist in the elderly with changes that are due to normal ageing. In such circumstances it may be impossible to separate the abnormalities in terms of their origin.

An important task for radiologists, when confronted with a brain study in an elderly patient, is to screen for the presence of neurodegenerative disorders. In this process, changes should not be attributed too easily to normal ageing. In order to be able to separate usual ageing and other neurodegenerative disorders, a radiologist should be familiar with the changes that occur in normal ageing. In the following section, such changes will be described.

Structured Evaluation of MRI in Workup of Dementia

1. Exclude a structural lesion which may be amenable for neurosurgical intervention. Consider both lesions with significant mass effect (e.g. subdural hematoma, meningioma) and lesions with minor mass effect (e.g. AVM).
2. Exclude brain swelling, either generalized swelling (e.g. associated with dural AVF or hydrocephalus) or focal swelling (e.g. medial temporal lobe swelling in HSV encephalitis). Whenever swelling is present, consider adding DWI and Gd-enhanced images.
3. Assess signal increase on T2/FLAIR, both in white matter (e.g. white matter changes (WMC) in vascular disease) and in grey matter (e.g. thalamic infarction in vascular disease or pulvinar sign in Creutzfeldt-Jakob disease). Consider applying a white matter rating scale, such as the Fazekas scale or the ARWMC scale. When describing vascular changes, assess/report specifically lacunes, état criblé and (bilateral) thalamic lesions and whether changes involve the brain stem or basal ganglia.
4. Assess microbleeds (MBs) on T2*GE, especially in subjects with white matter changes.
5. Determine the degree and pattern of general cortical atrophy (GCA) and specifically report whether the atrophy:
   (a) Is abnormal for age or not
   (b) Is symmetric of asymmetric
   (c) Has a regional pattern
   (d) Has a posterior or anterior gradient
6. Assess focal atrophy, especially in the following regions:
   (a) Medial temporal lobe (e.g. MTA as seen in AD) (see Table 2)
   (b) Temporal pole and/or frontal lobes (e.g. consistent with FTLD)
   (c) Biparietal atrophy (posterior cortical atrophy, mostly AD)
   (d) Occipital atrophy (posterior cortical atrophy or the Balint syndrome, usually AD but there is a considerable overlap with other neurodegenerative pathologies)
   (e) Posterior cingulate and precuneus (e.g. presenile or posterior AD)
   (f) Mesencephalic atrophy (e.g. PSP)
   (g) Pontine (and cerebellar) atrophy (e.g. MSA)
   (h) Cerebellar atrophy (e.g. alcohol abuse, prion, etc.)



AD: Alzheimer's diseasebvFTD: Behavioural varient frontot

Suggested Reading

Harper L, Barkhof F, Scheltens P, Schott JM, Fox NC (2014) An algorithmic approach to structural imaging in dementia. J Neurol Neurosurg Psychiatry 85(6):692

Frederik Barkhof, Nick C. Fox, António J. Bastos-Leite, Philip Scheltens (2002) Neuroimaging in dementia hardcover. Lancet Neurol 1(1):13–21

http://www.radiologyassistant.nl/en/p43dbf6d16f98d/dementia-role-of-mri.html