ADVANCED NEUROIMAGING: ACROSS LIFESPAN
Geriatric neuroimaging: white matter diseases of aging

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Several diseases of aging are associated with an increased frequency of lesions in the brain white matter (WM). Among these, vascular brain diseases are the most frequent. Cerebrovascular disease can be detected by computer tomography (CT) and structural magnetic resonance imaging (MRI). Although both modalities perform relatively well in depicting large-vessel infarcts, MRI is more sensitive to subtle small-vessel vascular changes than CT.

T2-weighted and FLAIR sequences are highly sensitive for detecting major strokes as well as small strategic infarcts and small-vessel ischaemic WM damage. FLAIR performs less well than T2-weighted sequences in detecting thalamic infarcts. Extensive WM changes visible as diffuse hyperintense abnormalities on T2 and FLAIR, predominantly involving the periventricular and deep WM, but relatively sparing of the U-fibres, are the imaging correlate of Binswanger's disease. Marked hypointensity on T1-weighted images usually represents tissue destruction in the presence of a complete large-vessel infarct, whereas WM changes are usually not prominently hypointense on T1-weighted images. Finally, lacunar infarcts are focal complete infarcts of deep small vessels, which are hyperintense on T2-weighted images and markedly hypointense on T1 and FLAIR images. On FLAIR, lacunae are often surrounded by a hyperintense rim. According to the National Institute for Neurological Disorders and Stroke Association pour la Recherche l'Enseignement en Neurosciences (NINDS-AIREN) international criteria, structural brain imaging is an essential element for the diagnosis of vascular dementia, and without it vascular dementia will be 'possible' at best. In addition, the operational radiological definitions for the NINDS-AIREN criteria provided indications on the topography and severity of vascular lesions. Bilateral infarcts in the area of the anterior cerebral artery, infarcts in the area of the posterior cerebral artery, association areas or watershed regions are thought to be causative of large-vessel vascular dementia. Extensive WM lesions involving at least 25% of the WM, or multiple basal ganglia, thalamic and frontal WM lacunar infarcts, or bilateral thalamic lesions, are considered relevant radiological lesions associated with small-vessel vascular dementia. Research criteria to specifically diagnose subcortical ischaemic vascular dementia have also been proposed: the presence of extensive periventricular and deep WM lesions and lacunar infarcts in the deep grey matter or multiple lacunae in the deep grey matter and at least moderate WM lesions, in the absence of cortical and/ or cortical–subcortical (non-lacunar) territorial infarcts, watershed infarcts, haemorrhages and other specific causes of WM lesions. Different methods can be used to measure the extent of WM changes to diagnose subcortical ischaemic vascular dementia. Visual rating of WM hyperintensities is relatively easy, and several scales are available with good reproducibility. Volumetric studies use semi-automatic techniques that may provide more information on location and size, as well as continuous data, but are time consuming. With the Age-Related White Matter Changes (ARWMC) scale, for instance, a score of 3 in at least two regions and a score of 2 in two other regions could be sufficient for a diagnosis of subcortical vascular dementia. A conversion table amongst some of the most popular scales to rate WM lesions can be found in Frisoni et al.

Cerebral microbleeds (or microhaemorrhages) are small, rounded, dot-like lesions of low signal intensity in the brain that can be observed on T2*-weighted images, such as gradient echo. Susceptibility- weighted imaging has considerably increased micro- bleed detection rates compared with gradient echo sequences. The sensitivity to detect microbleeds is also dependent on slice thickness and magnetic field strength. Microbleeds in deep brain regions are most likely to be associated with vasculopathy owing to hypertension, whilst their distribution is mostly lobar in specific disorders such as sporadic cerebral amyloid angiopathy (CAA). Sporadic CAA is the most common cause of lobar intracerebral haemorrhages in the elderly and results from cerebrovascular deposition of b-amyloid protein in the media and adventitia of small- and medium-sized vessels of the superficial layers of the cerebral cortex and leptomeninges, with sparing of the deep grey matter nuclei. According to a set of validated criteria (termed Boston criteria), a diagnosis of probable CAA can be reached in elderly patients with at least two acute or chronic lobar haemorrhagic lesions (including microbleeds), in the absence of other definite cause of intracerebral haemorrhage. The presence of extensive WM lesions and multiple bilateral, lacunar infarcts on T2-weighted and FLAIR images is critical for the diagnosis of cerebral autosomal dominant arteriopathy with sub- cortical infarcts and leucoencephalopathy (CADASIL), a genetic form of vascular dementia in relatively young people. The most distinctive MRI features suggestive of CADASIL are the presence of T2 hyperintensity of the temporal pole, the U-fibres at the vertex and external capsule or insular region, and multiple microhaemorrhagic foci (basal ganglia, internal capsule, thalamus and pons), which can be seen on gradient echo scans.

Although an increased WM lesion load suggests vascular disease, particularly in combination with lesions in the basal ganglia, a critical clinical challenge in subjects with vascular lesions is determining the relationship of cerebrovascular disease and cognitive symptoms. To appropriately diagnose vascular cognitive impairment or dementia, there should be a clear relationship in the severity and pattern of cognitive impairment and the presence of vascular lesions with neuroimaging. However, this association can be confounded by the frequent

co-occurrence of depression on a cerebrovascular basis, as well as by the frequent coexistence with neurodegenerative diseases, especially Alzheimer's disease (AD). Small-vessel disease is frequently observed in MRI scans of AD patients in the form of WM hyperintensities, lacunae and microbleeds. Several studies have indicated that the prevalence of microbleeds in AD ranges from 15% to 32%. Microbleeds are also considerably more frequent in AD compared with other neurodegenerative dementia. Of all the structural markers of AD, hippocampal atrophy assessed on conventional CT or coronal T1- weighted images is the best established and validated. Clinical population studies have reported that hippocampal volumes in mild AD patients are 15–40% smaller than controls, and in mild cognitive impairment (MCI) the volume is reduced by 10–15%.

No clear signature pattern of cerebral atrophy associated with dementia with Lewy bodies (DLB) has been established so far. Similar to AD, a diffuse pattern of global grey matter atrophy including temporal, parietal, frontal and insular cortices may occur in DLB, but at the same time, a pattern of cortical grey matter loss restricted to frontal and parietal lobes has also been reported. A relatively robust MR finding in DLB is that of relative preservation of the MTL compared with AD of similar clinical severity.

The terms FTLD and FTD describe a group of clinical syndromes which may be produced by a number of histopathologically distinct entities. The designation of probable behavioural variant of frontotemporal dementia (bvFTD) by the revised diagnostic criteria restricts diagnosis to patients with demonstrable functional decline and typical neuroimaging findings, including frontal and/or temporal atrophy, and hypoperfusion or hypometabolism on PET or SPECT. Structural MRI studies showed that classical bvFTD presents with a combination of medial frontal, orbital–insular and anterior temporal cortical atrophy. Such an atrophy pattern can be readily appreciated on coronal T1-weighted MRI scans (knife-edge atrophy). The MTL is more affected anteriorly, that is, the amygdala is more affected than the hippocampus, and posterior hippocampus often appears normal. Despite variation and overlap of atrophy patterns, visual inspection of regional atrophy on MRI may aid in discriminating FTD from AD. A combined diagnostic criterion based on the finding of either severe frontal atrophy or asymmetry was highly diagnostic (sensitivity 71%, specificity 93%) of bvFTD compared with non-FTD dementia cases (i.e. AD and vascular dementia).

Midbrain atrophy, better seen on sagittal T1-weighted images, dilatation of the third ventricle, atrophy of the superior cerebellar peduncle and frontal cortical atrophy support a diagnosis of PSP. T2-signal change in the superior cerebellar peduncle can be seen in PSP patients but is less sensitive. Quantitative MRI measurements of brainstem structures have been proposed as potentially useful markers to diagnose PSP on an individual patient basis. In particular, a ratio of linear measurements (e.g. the so-called MR parkinsonism index, which combines measurements of midbrain and pons areas as well as superior and middle cerebellar peduncle widths) has been shown to differentiate accurately PSP from Parkinson's disease (PD) and multiple system atrophy (MSA) cases. Other specific imaging signs may include bilateral striatal atrophy in Huntington's disease, sometimes many years before disease onset, and striatal or neocortical abnormalities in patients with CJD. In CJD, T2-weighted and especially FLAIR sequences can show a very characteristic pattern of hyperintense signal in the striatum and/or cortex. DWI can show focal changes in CJD not yet apparent on FLAIR images (up to 20% of cases). In sporadic CJD, involvement of either the striatum or neo- cortex or both is usually found. In variant CJD, there is a selective involvement of the medial and dorsal (pulvinar) thalamic nuclei, leading to the so-called hockey stick sign.

Based on the previous considerations, structural imaging should be carried out at least once in the diagnostic work-up of patients with cognitive impairment and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia.

A standard MRI protocol should include a high- resolution structural volumetric T1-weighted scan, transverse T2-weighted and FLAIR sequences and transverse T2*-gradient echo sequence. Routine contrast administration is not indicated. DWI can be useful to identify recent infarcts, as well as cortical and/ or basal ganglia changes in CJD patients.

It is particularly difficult to attribute clinical significance to evidence of cerebrovascular disease in patients with cognitive impairment. Vascular changes on CT or MRI do not preclude a diagnosis of degenerative dementia, especially in older age. A diagnosis of vascular dementia should only be made where the vascular lesion(s) can explain the cognitive deficit. The 'mixed dementia' label should be reserved for those cases in which both clinical features and diagnostic markers point to a mixed aetiology.

Future tools

Amyloid imaging

Of particular interest is the potential of PET amyloid imaging (currently just a research tool) to differentiate mixed AD with cerebrovascular disease from pure AD or vascular dementia. Both carbon-11 (11C) and 18F

ligands are available. One study found that 69% of patients clinically diagnosed with subcortical vascular dementia were negative for PET 11C-Pittsburgh compound B (PIB) binding. Younger age, a greater number of lacunae and a less severe MTL atrophy predicted a negative amyloid imaging scan. Another small study found high 11C-PIB binding in 40% of patients with post-stroke dementia. Thus, amyloid imaging can be helpful in identifying cognitively impaired patients with high vascular burden who also have comorbid AD. Furthermore, patients with CAA show high11C-PIB binding compared with controls, and this can aid differentiation between CAA and brain haemorrhages caused by small-vessel disease. Amyloid imaging such as 11C-PIB PET has very high (90% or greater) sensitivity for AD. Amyloid tracer binding is diffuse and symmetrical, with high uptake consistently found in the prefrontal cortex, precuneus and posterior cingulate cortex, followed by the lateral parietal, lateral temporal cortex and striatum. However, some healthy elderly controls show high 11C-PIB binding. The frequency of increased cortical 11C-PIB binding in controls increases rapidly from 10% or less below the age of 70 to 30–40% at the age of 80 years. As a group, 52–87% of MCI patients show elevated 11C-PIB binding in a similar regional distribution to AD.

Small case series using amyloid imaging reveal that DLB patients have often an increased cortical amyloid deposition (from 33% up to 87% of cases) similar to that observed in AD. The regional pattern of 11C-PIB retention in patients with DLB who were 11C-PIB-positive reflects the pattern typically seen in patients with AD, involving the frontal, parietal and superior temporal lobe association cortices. Increased striatal 11C-PIB retention has been reported in patients with DLB. Some degree of amyloid deposition is also observed in a minority of PD with dementia cases (from 17% to 33%), whilst it is more rarely present in PD patients without dementia (from 0% to 23%).

Amyloid imaging is expected to provide excellent differentiation of AD from FTD, which is not associated with amyloid deposition – particularly in younger patients.

Recommendations for amyloid imaging

Amyloid imaging is not yet recommended for routine use in the clinical setting, especially in the diagnostic work-up of patients with straightforward clinical AD as these patients are very likely to have positive scans.

Negative amyloid scans indicate absence of AD pathology with a high level of accuracy, but healthy elderly controls might have positive amyloid scans, so their predictive value in isolation is not clear.

Non-conventional MRI

1H-MRS Proton magnetic resonance spectroscopic imaging (1H-MRS) studies have reported that the level of N-acetylaspartate (NAA) is decreased in AD and MCI patients compared with healthy subjects. In addition to neuronal damage, increased glial cell activity, reflected by raised levels of myo-inositol (mI), has been demonstrated in AD patients compared with controls. The NAA/mI ratio enabled the differentiation of patients with AD from cognitively healthy subjects with relatively high sensitivity (57–90%) and specificity (73–95%).

Diffusion tensor (DT) MRI studies in AD have found altered diffusion properties compared with controls in several brain regions, especially in temporal and frontal lobes, posterior cingulum and corpus callosum. White matter changes in AD generally follow the anatomical pattern of grey matter atrophy. The severity of micro-structural damage within and beyond the MTL was associated with an increased short-term risk of developing AD in amnestic MCI patients.

Arterial spin labelling Non-invasive perfusion MRI with arterial spin label- ling (ASL) contrast uses magnetically labelled arterial blood water as an endogenous tracer to provide quantitative CBF measurements. Studies in patients with AD and FTD showed a pattern of hypoperfusion consistent with that of FDG PET hypometabolism. Similar findings have been found in amnestic MCI patients.

Suggested reading
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