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Review

Neuroimaging in dementia

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ABSTRACT

Over the last few years, advances in neuroimaging have generated biomarkers, which increase diagnostic certainty, provide valuable information about prognosis, and suggest a particular pathology underlying the clinical dementia syndrome. We aim to review the evidence for use of already established imaging modalities, along with selected techniques that have a great potential to guide clinical decisions in the future. We discuss structural, functional and molecular imaging, focusing on the most common dementias: Alzheimer's disease, fronto-temporal dementia, dementia with Lewy bodies and vascular dementia. Finally, we stress the importance of conducting research using representative cohorts and in a naturalistic set up, in order to build a strong evidence base for translating imaging methods for a National Health Service. If we assess a broad range of patients referred to memory clinic with a variety of imaging modalities, we will make a step towards accumulating robust evidence and ultimately closing the gap between the dramatic advances in neurosciences and meaningful clinical applications for the maximum benefit of our patients.

Contents

Abbreviations: 123-I-FP-CIT, 123-I labelled ioflupane (DatSCAN®); AD, Alzheimer's dementia; bv-FTD, behavioural variant fronto-temporal dementia; CERAD, consortium to establish a registry for Alzheimer's disease; CT, (X-ray) computed tomography; FTD, fronto-temporal dementia; LBD, dementia with Lewy bodies; lv-P, palogopenic variant PPA; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; NICE, National Institute for Health and Care Excellence; nv-PPA, non-fluent PPA; PET, positron emission tomography; PiB, Pittsburgh compound B; PPA, primary progressive aphasia; SPECT, single photon emission computed tomography; sv-PPA, semantic variant PPA; VBM, voxel-based morphometry; VD, vascular dementia; WMH, white matter magnetic resonance hyperintensities.

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1. Introduction

Over the last few years, advances in neuroimaging have generated biomarkers, which increase diagnostic certainty, provide valuable information about prognosis, and suggest a particular pathology underlying the clinical dementia syndrome. This is an advance over the role imaging plays in simply excluding rare causes of dementia, such as mass lesions [1,2]. Although the use of specific biomarkers is generally limited to research studies, it is likely to translate into clinical practice with increased standardization and access to biomarkers.

We aim to review the evidence for established imaging modalities, along with selected techniques that have the potential to guide clinical decisions in the future, focusing on the most common dementias: Alzheimer's disease (AD), fronto-temporal dementia (FTD), dementia with Lewy bodies (DLB) and vascular dementia (VD). Discussion of other dementia syndromes and the theory behind the various imaging modalities is beyond the scope of this review.

2. Structural imaging

2.1. Alzheimer's dementia

In many centres, X-ray computed tomography is the standard investigation to exclude any space occupying and mass lesions. In fact, some authors have used this technique to estimate hippocampal atrophy and thus provide added information supporting the diagnosis of Alzheimer's dementia [3]. However, the structural imaging technique most widely used in clinical research is T1-weighted magnetic resonance imaging (MRI). The most characteristic feature of AD is early, localized medial temporal lobe atrophy (MTA) affecting primarily the hippocampus and entorhinal cortex [4–8]. MRI evidence of disproportionate MTA has been incorporated into revised diagnostic criteria as a topographical marker of downstream neuronal injury [1,2].

In clinical practice visual assessment is used most often. One of the more widely validated rating scales is the Scheltens' MTA rating scale [9], which assesses hippocampal atrophy according to the width of the choroid fissure, width of the temporal horn, and height of the hippocampus, using a 0–4 severity scale. *Visual inspection* differentiates mild AD from normal ageing with a sensitivity and specificity of 80–85% [9–11]. The specificity of MTA decreases with age because of age-related hippocampal atrophy [12]. In research studies, mainly *volumetric techniques* are used and they appear to correlate well with both neuropathological disease progression [13–15] and the degree of cognitive impairment [16,17].

Although MTA has been found in other dementias, including FTD, VD and PD, it is less severe there than in AD when matched for clinical severity [18,19]. Hippocampal atrophy develops gradually starting about 5 years before diagnosis of AD, while 3 years prior to diagnosis hippocampal volumes are reduced by 10% [19].

In atypical forms of AD, in younger patients, or early in the disease course it is possible to have greater atrophy of the parietal lobes and less MTA [20–25]. A rating scale based on the degree of widening of the posterior cingulate, parietal and parieto-occipital sulci has been developed [26].

Particularly in individuals with MCI, structural imaging provides valuable information about prognosis. Although the significant overlap in volumetric measures between patients with MCI and controls sets some limitations, a recent meta-analysis of 6 VBM studies found that decreased grey matter in the left hippocampus and parahippocampal gyrus was associated with conversion from MCI to AD [27]. Further, Lehmann et al. [28] found that the probability of converting from MCI to AD increased with greater baseline MTA scores; e.g. after three years, fewer than 40% of patients with an MTA score of 0 converted to AD, compared with more than 75% with baseline MTA score of 3.

2.2. Fronto-temporal dementia

FTD encompasses a heterogeneous group of conditions and can be broadly divided into behavioural variant fronto-temporal dementia (bv-FTD) and primary progressive aphasia (PPA). Bv-FTD is associated with predominant atrophy in the frontal and paralimbic areas, including the anterior cingulate cortex, as well as orbitofrontal and medial frontal cortices and subcortical structures [29–32]. Ratings of orbitofrontal atrophy in conjunction with an executive function test classified 92% of patients correctly into bvFTD or AD [33].

PPA is itself categorized into three clinical phenotypes: semantic variant PPA (sv-PPA), non-fluent PPA (nv-PPA) and logopenic variant PPA (lv-PPA). In semantic variant PPA, there is typically atrophy of the anterior and inferior temporal lobes, including the fusiform gyrus, while the non-fluent variant PPA is characterized by perisylvian atrophy and involvement of the anterior insula [31,34,35]. The logopenic variant PPA is commonly associated with Alzheimer's type pathology and the atrophy involves the posterior temporal cortex and inferior parietal lobule [36]. In PPA the atrophy is more often asymmetrical, with the left side being more affected [31]. In addition to distinct patterns of regional atrophy that are associated with each clinical phenotype, rate of atrophy was found to be twice as great in FTD and SD, compared with AD [37]. However, in the early stages, functional imaging may be more useful because the structural scan can be normal [32,38]. The most recently published guidelines for FTD proposed, in addition to a clinical diagnosis, evidence for abnormalities on either structural or functional brain imaging as a criterion for establishing a diagnosis of 'probable' FTD [36,39].

2.3. Dementia with Lewy bodies

DLB is associated with diffuse atrophy, which is greater than in controls, but less than in patients with AD. Relatively focused dorsal meso-pontine grey matter atrophy, with a relative sparing of the medial temporal lobes, supports a clinical diagnosis of DLB rather than AD [40–42].

2.4. Vascular dementia

Evidence from structural neuroimaging is mandatory for diagnosing vascular dementia (VD), with MRI being the preferred modality. Small-vessel disease is the commonest cause of VD [43], although large artery ischaemic disease may lead to VD, as well.

Small-vessel disease is usually defined as lesions involving >25% of the white matter. Signs of small vessel disease on MRI include white matter magnetic resonance hyperintensities (WMH), recent small subcortical infarcts, lacunes, prominent perivascular spaces, cerebral microbleeds and atrophy. Their defining features are summarized in an excellent paper aiming to provide standards for reporting vascular changes on neuroimaging (STRIVE [44]). Although white matter changes can be detected on X-ray CT scans, the tissue contrast tends to be discrete, and this method is less sensitive than MRI.

White matter lesions appear as bilateral, mostly symmetrical hyperintensities on T2-weighted MRI. They become more common with advancing age and are found in 10–90% of cognitively normal elderly depending on the study. Although WMH are strongly associated with vascular risk factors, as well as predicting an increased risk of stroke and dementia [45], they are clinically and pathologically heterogeneous [46]. WMH are not specific to vascular dementia and can be found in a variety of other conditions