Structural and molecular imaging in dementia: the heterogeneity of Alzheimer's disease

Main text (623 words)

Alzheimer's disease (AD) is the most common cause of dementia. The most frequent clinical presentation is with memory decline, followed by impairments in other domains (and thus fulfilling the criteria for dementia). Typical findings in amnestic AD are medial temporal lobe atrophy (MTA) which can be appreciated using visual rating of coronal MRI (and CT) scans [1]. In younger patients, however, the initial presentation tends to be more frequently with visuospatial and visuoconstructive disturbances (e.g. lack of orientation and reading) associated with atrophy of especially the parietal and sometimes occipital lobe, best appreciated on sagittal MRI/CT scans. The combination of these clinical/radiological findings is referred to as posterior cortical atrophy (or PCA) and such patients are less likely to be APOE4 carriers. Finally, atypical presentations of AD include behavioural and language variants with more frontal patterns of atrophy. While structural MRI is important to highlight regional atrophy patterns that are associated with AD, each of them present with a differential diagnosis; e.g. PCA can be due to Lewy body dementia, requiring molecular imaging techniques such as dopamine imaging for confirmation [1,2].

Short of confirmation of AD at autopsy, demonstration of amyloid (and tau) pathology using CSF biomarkers or PET is increasingly important for the diagnosis of AD, certainly now disease modifying anti-amyloid therapies are on the horizon [3]. CSF has the advantage of allowing assessment of both amyloid and tau simultaneously, while PET shows the distribution of either amyloid or tau throughout the brain. Plasma assays for tau are improving rapidly, while accurate plasma assays for amyloid are lagging in their development. By combining information about amyloid (A) and tau (T) markers with those for neurodegeneration (N, e.g. from structural imaging), it is possible to classify patients in the so-called ATN framework [4]. While developed to better operationalize the diagnosis of AD pathology in a research setting, the use of biomarker information (including PET) is increasingly incorporated in clinical diagnostic criteria. It is important to realize that subjects may become A+ decades before the onset of dementia (referred to as preclinical Alzheimer pathological changes) and its positive predictive value therefore is low. On the other hand, a normal A- status rules out AD definitively [5]. A+T+ subjects (referred to Alzheimer's disease) are much more likely to be symptomatic and a positive tau-PET usually occurs close to the time of onset of symptoms. In patients with atypical presentations of AD as discussed above, tau-PET studies have revealed quite diverse patterns of neocortical tau deposition, largely reflecting the clinical syndromes [6].

At the other end of the spectrum are subjects with clear signs of hippocampal neurodegeneration on structural imaging but with normal A (and even T) staging; such A-T-N+ subjects are likely to have non-Alzheimer type of neurodegeneration. One example is so-called LATE (Limbic-predominant age-related TDP-43 encephalopathy) that both clinically and radiologically manifests identical to amnestic AD [4]. A diagnosis of LATE should be considered in very old patients and such patients obviously would not be good candidates for anti-amyloid therapy.

Is there still a role for structural imaging in the molecular area? Molecular imaging clearly is more specific, but the use of PET will come with safety, cost, and logistic barriers. CSF and perhaps plasma analysis are more likely candidates to fill that gap. Structural imaging will still be required to rule out surgically treatable disorders, rule out vascular co-pathology and alternative neurodegenerative patterns (where amyloid could be an incidental finding). For the latter, it is important to systematically evaluate MRI scans and visual ratings scales can be a useful adjunct [7]. Finally, MRI

demands will soar when anti-amyloid treatment is introduced clinically to screen out subjects with contraindications (multiple microbleeds or superficial siderosis) or to detect side-effects in the form or ARIA (amyloid-related imaging abnormalities) [8].

References

1) Haller, S., Garibotto, V., Barkhof, F. (2019). Neurodegenerative Disorders: Classification and Imaging Strategy. In: Barkhof, F., Jäger, H., Thurnher, M., Rovira, À. (eds) Clinical Neuroradiology. Springer, Cham. https://doi.org/10.1007/978-3-319-68536-6_78

2) Villemagne VL, Barkhof F, Garibotto V, Landau SM, Nordberg A, van Berckel BNM. Molecular Imaging Approaches in Dementia. Radiology. 2021 Mar;298(3):517-530

3) van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21

4) Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018 Apr;14(4):535-562

5) Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. Neurology. 2011 Dec 6;77(23):2034-42

6) Ossenkoppele R, Schonhaut DR, Schöll M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain. 2016 May;139(Pt 5):1551-67

7) Vernooij MW, Pizzini FB, Schmidt R, et al. Dementia imaging in clinical practice: a European-wide survey of 193 centres and conclusions by the ESNR working group. Neuroradiology. 2019 Jun;61(6):633-642

8) Cogswell PM, Barakos JA, Barkhof F, et al. Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice. AJNR Am J Neuroradiol. 2022 Sep;43(9):E19-E35