The role of biomarkers and imaging in the clinical diagnosis of dementia

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Abstract

Recognition of dementia relies on a good clinical history, supported by formal cognitive testing, but identifying the subtype of dementia may be wrong in 20% or more of cases. Accuracy may be improved by use of imaging and cerebrospinal fluid (CSF) biomarkers. Structural neuroimaging is recommended for most patients, not just to identify potentially reversible surgical pathology, but also to detect vascular changes and patterns of cerebral atrophy. Functional imaging can help to confirm neurodegeneration and to distinguish dementia subtypes when structural imaging has been inconclusive. Amyloid-PET scans reflect neuritic plaque burden and identify the earliest pathological changes in Alzheimer's disease, but their value outside research settings is still uncertain. A combination of low CSF amyloid $\beta_{1\text{-}42}$ and high CSF total-tau or phospho-tau also has high predictive power for AD pathology, but diagnostic usefulness decreases with age because of the increased prevalence of AD-type pathology in non-demented people. The need to use biomarkers more routinely will become necessary as disease-modifying treatments become available and accurate subtype diagnosis will be required at an early (ideally pre-dementia) stage. Clinicians should be considering the resources and expertise that will soon be needed for optimal dementia diagnosis.

Keywords: dementia, neuroimaging, biomarkers, clinical diagnosis

Diagnosis of the dementia syndrome (now subsumed under the broader category of major neurocognitive disorder in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders – DSM-5 [1] is usually straightforward. It depends upon a reliable clinical history of significant decline in memory or other cognitive ability that is so severe that it interferes with ability to undertake everyday activities. No special tests are required, although formal cognitive testing is appropriate to confirm underperformance.

Determining the subtype of dementia is more challenging, but a necessary step as the specific cause of dementia will impact upon treatment and prognosis. Even in expert hands, clinical diagnosis of Alzheimer's disease (AD) dementia will be wrong in about 20% of cases [2]. Accuracy of diagnosis of vascular dementia is probably even worse, especially in the oldest-old when pure vascular pathology is uncommon and multiple pathology becomes the norm [3].

The past twenty years have seen the emergence of a range of biomarkers that are indicative or supportive of the pathology underlying a patient's dementia syndrome. Investigations are no longer undertaken solely to exclude potentially reversible causes, such as a space occupying lesion, but are now part of the diagnostic process and have become incorporated into most recent consensus guidelines for diagnosis of AD [4] and dementia with Lewy bodies (DLB) [5].

Currently available biomarkers either identify the nature and spatial distribution of pathological changes in the brain (e.g. structural and functional imaging) or identify presence of specific pathology (e.g. amyloid or tau positron emission tomography (PET) and

cerebrospinal fluid (CSF) markers). A recent "A/T/N classification", using biomarkers alone rather than clinical symptoms to describe AD pathophysiology across the asymptomatic to dementia spectrum, has even been suggested. In this system, "A" refers to positive amyloid biomarkers (the earliest change in AD), "T" to tau biomarkers and "N" to markers of neurodegeneration [6].

Structural imaging

Structural neuroimaging with magnetic resonance imaging (MRI) or computerised tomography (CT) is recommended to assist with diagnosis in most cases of dementia, except perhaps in the very frail and those whose dementia is already very advanced. Ideally a standardised protocol for acquisition and structured approach to analysis should be used. This will identify the extent and characteristics of any vascular changes and the presence of other non-degenerative pathology (e.g. tumour, normal pressure hydrocephalus, subdural haematoma), as well as the patterns of cerebral atrophy that occur in typical (amnestic) or atypical AD, or in the frontotemporal dementias (FTDs). Absent or minimal imaging evidence of medial temporal lobe atrophy will be typical in DLB.

There is consensus that evidence of cerebrovascular disease is essential for diagnosis of probable vascular cognitive impairment [7], but evidence of vascular change (particularly the ubiquitous report of 'evidence of small vessel disease') does not preclude diagnosis of neurodegenerative disease.

Whilst clinical guidelines suggest MRI is the modality of choice to assist with early diagnosis, especially in younger-onset cases, CT is generally more accessible and may be more acceptable to elderly patients. The evidence that MRI is better than CT for detecting a vascular component to dementia is limited [8] and a routine policy of CT followed by MRI for patients with space occupying lesions is likely to be most economic.

Functional imaging

Functional imaging reflects cerebral metabolic activity and so identifies characteristic patterns of hypometabolism associated with neurodegeneration even early in disease, either directly with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) or indirectly by measuring blood flow with ^{99m}Tc- hexamethylpropyleneamine oxime single photon positron emission CT (HMPAO-SPECT). Compared to PET, SPECT is less sensitive and specific [9], but still far more accessible and so of value in routine clinical practice to confirm neurodegeneration and to distinguish dementia subtypes when structural imaging has been inconclusive.

Reduced dopamine transporter (DaT) uptake in basal ganglia demonstrated by ^{123}I FP-CIT SPECT or PET imaging has good sensitivity and specificity for distinguishing DLB from AD and is an indicative biomarker of DLB (along with ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy) in the latest consensus criteria [5].

Molecular imaging

In vivo imaging of amyloid and more recently of tau has transformed dementia research in the past decade, allowing the identification of the very earliest pathological changes in AD, up to twenty years before the development of dementia. The ^{18}F-labeled PET tracers, florbetapir, flutemetamol and florbetaben, bind to fibrillar amyloid-β aggregates and reflect neuritic plaque burden.

In research settings, all have excellent sensitivity and specificity for differentiating clinically or pathologically diagnosed AD from healthy controls [10]. However, their additional diagnostic value over standard procedures in clinical settings is far less certain. Meta-analyses of available biomarker studies have reported prevalence of amyloid positivity increased from age 50 to 90 years from 10% to 44% among participants with normal cognition [11] and in non-AD dementias, amyloid positivity also increased with age, up to 83% in apolipoproteinE e4 carriers with DLB and up to 64% in vascular dementia cases at age 80 [12]. This likely reflects the multiple pathology that is characteristic of dementia presenting in the oldest old [3].

Although licensed in United States and Europe, current recommendations for amyloid-PET suggests clinical use should be restricted to dementia experts and for patients with early onset and atypical AD presentations, or for differentiating AD from FTD when comprehensive work-up has been inconclusive. Whilst a negative amyloid-PET scan excludes the diagnosis of AD, it does not exclude other causes of dementia and the disclosure of either a positive or negative scan result to patients needs to be delivered sensitively. It seems likely that amyloid-PET will have greatest utility in the preclinical stages of AD, identifying people most likely to benefit from disease-modifying interventions. The clinical

role of tau-PET has yet to be established, but it may prove to be of especial value given the close correlation between extent of neurofibrillary tangles and dementia severity.

Fluid biomarkers

The "core" CSF biomarkers of AD are amyloid $\beta_{1\text{-}42}$ (which is inversely related to the degree of amyloid burden in the brain), total-tau (reflecting neuronal degeneration) and phospho-tau (reflecting neurofibrillary tangle density). Whilst each independently predicts AD pathology, diagnostic sensitivity and specificity is greatest with a combination of low amyloid $\beta_{1\text{-}42}$ and high total-tau or phospho-tau [13]. The ratio of amyloid $\beta_{1\text{-}42}$ to amyloid $\beta_{1\text{-}40}$ also performs well. As with amyloid imaging biomarkers for AD, diagnostic accuracy of CSF biomarkers decreases somewhat with age because of the increased prevalence of AD-type pathology in non-demented people [14].

High CSF total-tau reflects intensity of neuronal damage and so is not specific to AD, but may also occur after brain trauma, acute stroke or in Creutzfeldt-Jakob disease. CSF levels of neurofilament light chain (NfL), another marker of neuronal injury, are raised in all neurodegenerative dementias, but markedly so in FTD syndromes [13].

Uptake of CSF biomarkers has been hampered by the necessity for lumbar puncture, though they are less costly and potentially more widely available than amyloid imaging. There have also been problems with standardizing analysis of samples and it is important to collect CSF in tubes made of polypropylene rather than the usual polyethylene, to avoid underestimating amyloid $\beta_{1\text{-}42}$ levels [13].

Much time and effort have been invested in looking for a less invasive, cost-efficient and so likely more acceptable blood-based biomarker, but so far with limited success. Unfortunately, plasma beta amyloid and tau levels do not mirror their CSF counterparts.

Conclusions

In dementia research, positive biomarkers have become a requirement for participant recruitment in disease-specific trials and they are also widely used to verify drug-target engagement and as surrogate markers of treatment efficacy. Whether their widespread use in current clinical practice would significantly affect diagnostic decisions or change management is less certain. Proving cost-effectiveness will be a challenge given that most of the costs of dementia occur many years after diagnosis.

Furthermore, the specific biomarker patterns associated with each dementia subtype are derived from group differences and there is considerable overlap between them. Caution is appropriate therefore when applied to an individual case. This is especially so in the oldest-old [15], who are the very age group with growing numbers developing dementia. Younger-old cases have fewer comorbidities and there is closer correlation between neuropathological changes and clinical features and so biomarkers are likely to be of greatest clinical value.

The need to use biomarkers routinely will soon become necessary as disease-modifying treatments start to become available and there is an unarguable need to characterise clinically relevant brain changes and to make diagnosis at an early (ideally pre-dementia)

stage. Clinicians need to start considering if current diagnostic services are fit-for-purpose and have adequate resources, experience and access to use and interpret biomarkers appropriately as part of the optimal dementia diagnostic pathway.

Key points

- The accuracy of clinical diagnosis of dementia subtype is improved by use of neuroimaging or CSF biomarkers.
- Biomarkers are generally less accurate the older the patient.
- Molecular imaging with amyloid scans for AD diagnosis has become routine in research settings, but it is still premature to consider its more widespread clinical use.
- Clinicians should be considering the resources and expertise that will soon be needed for optimal dementia diagnosis.

Conflict of interest

None declared

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