
2.1 Introduction

AD accounts for up to 75 % of all dementia cases. The differential diagnosis with other conditions is sometimes challenging since several disorders may produce similar symptoms to AD, including cortical basal degeneration (CBD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), frontotemporal lobe dementia (FTLD), vascular dementia (VaD), multiple-system atrophy (MSA) and progressive supranuclear palsy (PSP), among others.

Knowing the key features and pathology of each type of dementia can help in accurate diagnosis, so that patients will receive the treatment and support services appropriate for their condition and maintain the highest possible quality of life (Table 2.1) (Seeley and Miller 2013).

However, biomarkers able to differential between dementing conditions would be very useful in clinical practice. Indeed, today there is evidence that some biomarkers can play a role in the differential diagnosis of AD against other dementias (Table 2.2).

2.2 CSF Biomarkers

CSF A β 42, t-Tau, and p-Tau are useful in differential diagnosis of dementing disorders, including AD, DLB, FTLD, VaD, CBD,

Creutzfeldt-Jakob disease, psychiatric disorders, and subjective memory complaints (SMC). One must be aware, however, that there is some overlapping in the proteinopathies behind the different neurodegenerative disorders, and this fact is translated in the level of CSF proteins. For instance, CSF Tau elevation may be observed also in other diseases, being implicated pathologically in PD, PSP, and CBD (Zhang et al. 2013), potentially limiting the utility of Tau alone in the differential diagnosis of dementia. Nevertheless, the p-Tau/A β 42 ratio is a useful tool to discriminate AD from both FTLD and semantic dementia (SD) (de Souza et al. 2011). Regarding the different proteinopathies behind the most frequent neuropathological subtypes of FTLD (Tau and TDP), CSF measurements of A β 1–42, t-Tau, and p-Tau in FTLD differ significantly from the abnormal levels seen in AD, and in a subset of both FTLD-Tau and FTLD-TDP there are extremely low levels of t-Tau of unclear etiology. These properties allow for accurate distinction of FTLD from AD in autopsy-confirmed cohorts, though FTLD-specific markers are still lacking (Irwin et al. 2013).

Synucleinopathies (PD, DLB, MSA) are caused by the accumulation of α -synuclein in the brain. CSF levels of α -synuclein are decreased in patients with PD, DLB, and MSA but increased in patients with AD; thus CSF α -synuclein differentiates these synucleinopathies from AD (Wennström et al. 2013; van Dijk et al. 2013).

Table 2.1 Clinical differentiation of the major dementias

Disease	First symptom	Mental status	Neuropsychiatry	Neurology	Imaging
AD	Memory loss	Episodic memory loss	Initially normal	Initially normal	Entorhinal cortex and hippocampal atrophy
FTLD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy, disinhibition, hyperorality, euphoria, depression	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; spares posterior parietal lobe
DLB/ PDD	Visual hallucinations, REM sleep disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
Vascular dementia	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter

AD Alzheimer's disease, CBD cortical basal degeneration, DLB dementia with Lewy bodies, FTLD frontotemporal lobe dementia, MND motor neuron disease, PSP progressive supranuclear palsy, PDD Parkinson's disease dementia, REM rapid eye movement

Table 2.2 Biomarkers potentially useful in the differential diagnosis of AD against other dementias

Other dementia	Useful biomarkers
Parkinson's disease dementia	CSF α -synuclein, amyloid
Dementia with Lewy bodies	Medial temporal atrophy on MRI, CSF α -synuclein
Frontotemporal lobe dementia ^a	CSF p-Tau/A β 42 ratio, medial temporal atrophy on MRI, amyloid, FDG PET
Multiple-system atrophy	CSF α -synuclein
Primary progressive apraxia	Medial temporal atrophy on MRI
Vascular dementia	Amyloid, CSF p-Tau/A β 42 ratio

^a The three clinical subtypes show different patterns of hippocampal atrophy: (1) Semantic dementia shows bilateral hippocampal atrophy, although the left hippocampus tends to be smaller than in AD. (2) The behavioral variant (bvFTD) group showed significant white matter contraction, and the presence of behavioral symptoms at baseline predicted significant volume loss of the ventromedial prefrontal cortex (Lu et al. 2013). (3) No significant hippocampal atrophy was detected in nonfluent progressive aphasia (van de Pol et al. 2006)

CSF cerebrospinal fluid, FDG PET fluorodeoxyglucose positron emission tomography, Amyloid represents both CSF amyloid and amyloid PET SCAN

2.3 Neuroimaging

2.3.1 MRI

By highlighting specific topographical patterns of atrophy, neuroimaging using MRI has the potential to be useful in discriminating between different types of dementia. Presently, scanner

manufacturers are developing radiological expert systems based on indices and ratios to help in rating the presence or absence of AD from the pattern of atrophy derived from a single brain scan. The major impetus for the development of methods of temporal lobe assessment has been to improve the accuracy of early diagnosis in AD, yet it is unclear whether medial temporal lobe atrophy is specific for AD or can also be a feature of other

dementias, as few studies to date have compared patients with AD with patients having other forms of degenerative disease, such as FTLT.

Several studies support the hypothesis that a greater burden of pathology centers on the temporal lobes in AD compared with DLB, except in DLB cases with concurrent AD pathology (Barber et al. 1999; Tam et al. 2005; Burton et al. 2009). Unlike findings reported in younger subjects, visual ratings for posterior cortical atrophy are not a reliable marker at older ages for distinguishing AD from controls, or for distinguishing DLB from AD (O'Donovan et al. 2013). However, visual ratings of medial temporal lobe atrophy (MTA) may be useful markers in distinguishing both AD and DLB in older patients without dementia. Similarly, more objective methods such as the MTA index (MTAi) or volumetric studies are expected to be useful in the differential diagnosis of AD against other neurodegenerative dementias in a wider range of ages.

2.3.2 FDG PET

Regarding differential diagnosis, [18F]fluorodeoxyglucose (FDG) PET has shown great value because it allows the detection of different patterns of neurodegeneration that are specific for various non-AD (amyloid-negative) forms of neurodegeneration. These include the subtypes of FTLT, as well as MSA, CBD, and PSP (Yamane et al. 2013). Most importantly, FDG PET is also highly useful in differentiating within amyloid-positive subtypes of disease, which cannot be distinguished on the basis of their amyloid PET scan. This includes Lewy-body dementia (Kasanuki et al. 2012; Lim et al. 2009; Ishii et al. 2007), posterior cortical atrophy, and the logopenic variant of progressive aphasia (Fig. 2.1) (Madhavan et al. 2013; Mosconi et al. 2008).

2.3.3 Molecular Neuroimaging

Most molecular tracers used in AD research are considered to be specific for amyloid deposition, with the exception of FDDNP, which has been

demonstrated to bind also to Tau aggregates apart from amyloid. Although the tracers are specific for the protein aggregation (i.e., amyloid plaques), it is important to remember that the protein aggregation is not specific for AD. For example, it is known from histopathological studies that aggregation of amyloid plaques is found in the brain of most patients with DLB, in addition to the pathognomonic synuclein deposits. Thus, amyloid imaging may not be able to differentiate between DLB and AD. Furthermore, amyloid imaging alone may not be helpful with regard to distinguishing between amyloid-positive subtypes of AD (typical AD, the logopenic variant of progressive aphasia, and posterior cortical atrophy).

A negative amyloid-PET scan indicates few or no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition. Thus, it also reduces the likelihood that a patient's cognitive impairment is due to AD. On the other hand, a positive amyloid-PET scan indicates moderate to frequent amyloid neuritic plaques. Such scans may be observed in older people with normal cognition and in patients with various neurologic conditions, including AD. Therefore a positive scan alone does not establish a diagnosis of AD or other cognitive disorder, although it may be useful in combination with other clinical parameters. Pittsburgh Compound B (PiB) and FDG are similarly sensitive in discriminating between AD and FTLT. PiB is more sensitive when interpreted qualitatively or quantitatively. FDG is more specific, but only when scans are classified quantitatively (Rabinovici et al. 2011).

2.4 Key Concepts

1. There is some overlap among the proteins accumulated in various neurodegenerative disorders, and this fact is translated in the level of CSF proteins, limiting the utility of such measures in the differential diagnosis of dementia.
2. Several CSF proteins are useful in the differential diagnosis between the

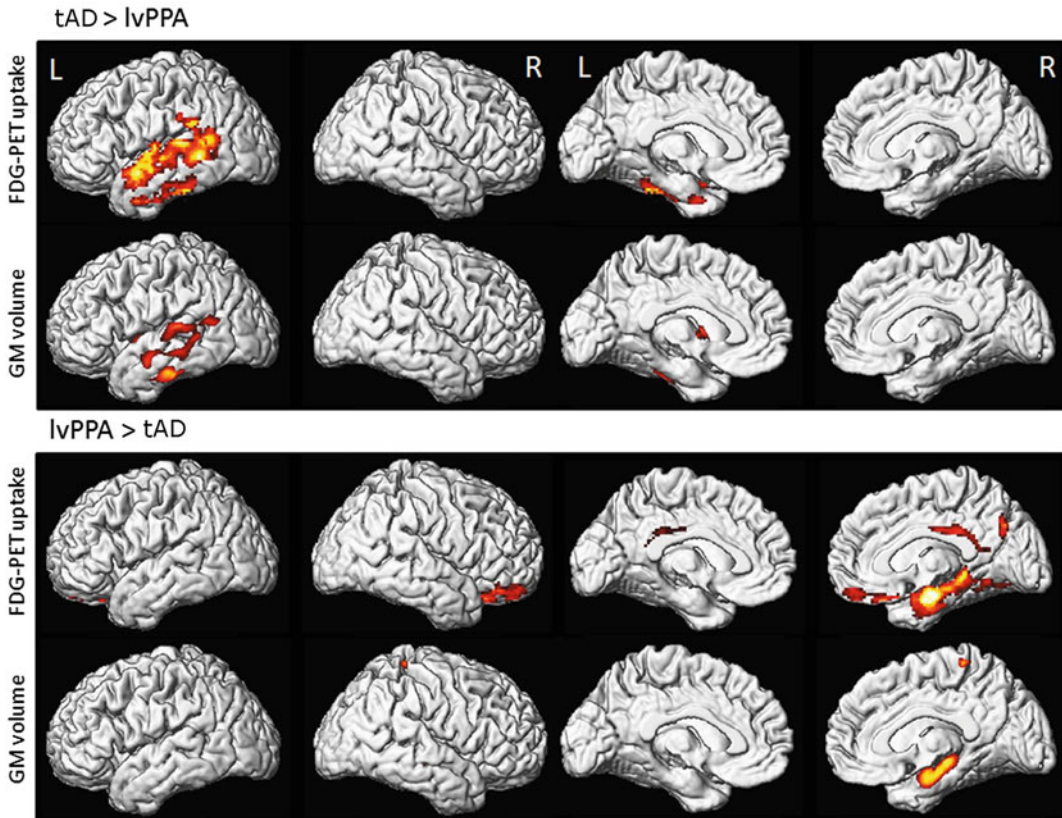


Fig. 2.1 Voxel-level imaging comparison of the logopenic variant of primary progressive aphasia (lvPPA)—an atypical clinical variant of Alzheimer's disease—and typical Alzheimer's type (tAD). A higher degree of

atrophy was observed in lateral temporoparietal and medial parietal lobes, left greater than right, and left frontal lobe in the logopenic group (from Madhavan et al.)

neurodegenerative disorders causing dementia, however. For instance, the p-Tau/A β 42 ratio is a useful tool to discriminate AD from FTLD.

3. CSF α -synuclein is useful in the differentiating AD from PDD, DLB, and MSA.
4. Hippocampal atrophy is not specific for AD, but it is useful to differentiate AD from DLB.
5. There are some differences between the profile of hippocampus atrophy found in AD and the profile found in the different types of FTLD.
6. A negative amyloid PET scan rules out AD with high predictive value.

7. PiB and FDG PET scans are useful in discriminating AD from FTLD. FDG PET is also useful for differentiating AD from DLB.

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