Alzheimer's disease and frontotemporal dementia: prospects of a tailored therapy?

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Dementia is defined as a chronic or progressive loss of cortical and subcortical functions resulting in a complex cognitive decline. This is commonly accompanied by disturbances of mood, behaviour and personality. Because of increasing life expectancy, neurodegenerative dementias are becoming more common. In developed countries, the prevalence of dementia is 1.5% among 65-year-olds, doubling with every 4 years of increasing age to reach 30% among 80-year-olds.[1] Alzheimer's disease (AD) is the most prevalent of the dementias (accounting for 50%–75% of cases), followed by frontotemporal dementia (FTD) (10%–20%), vascular dementia (10%–15%) and dementia with Lewy bodies (10%–15%).[2] The social and economic burden associated with these dementias is enormous. Currently, 160 000 Australians are affected, but with the ageing of the population, this will increase to an estimated 500 000 by 2040. The annual cost to the Australian economy is about $6.5 billion, corresponding to 1% of the gross domestic product, and is estimated to reach 3.3% by the middle of this century.[3]

ABSTRACT

- Alzheimer's disease (AD) is the most prevalent dementia (accounting for 50%–75% of cases of dementia in people aged over 65 years), followed by frontotemporal dementia (FTD) (10%–20% of cases).
- AD is characterised histopathologically by Aβ-containing amyloid plaques and tau-containing neurofibrillary tangles, whereas FTD exhibits neurofibrillary tangles alone.
- Current symptomatic treatments of AD are of limited benefit, as they are not directed at the underlying biological basis of the disease.
- The development of transgenic animal models has provided insight into disease mechanisms and helped define novel drug targets.
- More than 50 drugs are currently in clinical trials, and novel and more effective drugs targeting both AD and FTD are expected to become available within 5–10 years.

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Limitations of current treatment

The current symptomatic treatment of AD is of limited benefit, as it is not directed at the underlying biological basis of the disease. Treatments include the acetylcholine esterase inhibitors (eg, donepezil hydrochloride, galantamine hydrobromide and rivastigmine tartrate), which stabilise the neurotransmitter acetylcholine in the synaptic cleft, and the *N*-methyl-*D*-aspartate receptor antagonist, memantine, which counteracts the deleterious effects of high brain concentrations of the excitatory amino acid, glutamate. Unfortunately, these drugs can have severe psychotropic side effects in patients with FTD.[4] Treatment in general is further complicated by the fact that FTD is very heterogeneous, comprising several clinical entities.[5,6]

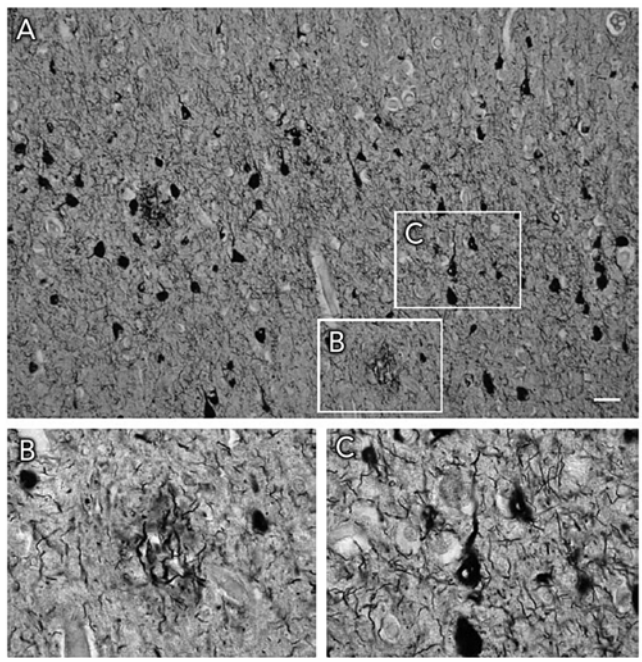
Biological basis of AD and FTD

Histopathologically, both AD and FTD are characterised by insoluble filamentous aggregates in the brain (Box 1). They share this feature with Parkinson's disease and Creutzfeldt–Jakob disease. The biological basis of AD and FTD is discussed in Box 2. As both diseases involve lesions containing the microtubule-associated protein tau, they are classed as tauopathies (see Box 3 for definitions). AD is characterised histopathologically by Aβ-containing amyloid plaques and tau-containing neurofibrillary tangles, whereas FTD exhibits neurofibrillary tangles alone.

Clinical features

The clinical presentation of AD is dominated by early memory deficits, followed by gradual erosion of other cognitive functions such as judgement, verbal fluency or orientation. Memory impairment is usually the first and dominating feature and reflects the fact that the most severe neuropathological changes occur in the

1 Hallmark lesions of Alzheimer's disease and frontotemporal dementia



A: *Temporal lobe of the brain in Alzheimer's disease, revealing neurofibrillary tangles and neuritic plaques (Gallyas silver stain; scale bar, 12.5μm).* ***B:*** *Neuritic plaque at higher magnification.*
C: *Neurofibrillary tangle with sparing of the nucleus (centre) at higher magnification. Amyloid plaques are virtually absent in frontotemporal dementia, which thus can be considered a tau-only tauopathy.* ◆

hippocampal formation, followed by the association cortices and subcortical structures.

FTD is the preferred term for a spectrum of dementias characterised by focal atrophy of frontal and anterior temporal regions. FTD is mainly associated with behavioural impairment (such as unrestrained behaviour resulting from a lessening or loss of inhibitions and personal and social awareness), followed by affective symptoms, speech disorder and memory problems. In many cases, additional degenerative changes are observed in subcortical brain regions, such as the substantia nigra, leading to Parkinsonian symptoms.[16-18] One

2 Histopathology and genetic basis of Alzheimer's disease and frontotemporal dementia

Alzheimer's disease (AD) was initially defined by the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (Box 1).

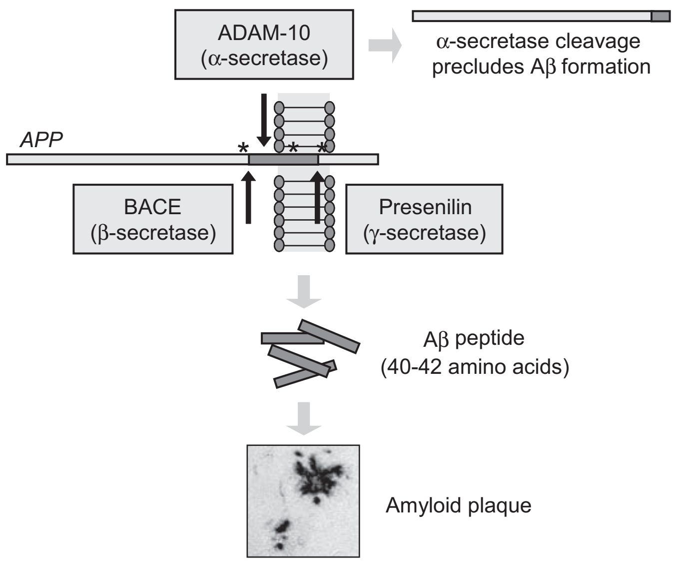
Amyloid plaques: The major component of amyloid plaques is Aβ, an aggregated peptide comprising 40–42 amino acids ($A\beta_{40}$ and $A\beta_{42}$). This peptide is derived by proteolytic cleavage from the larger amyloid precursor protein. The precursor protein is cleaved first by β-secretase and then by γ-secretase, which together generate the Aβ peptide. β-Secretase activity has been attributed to a single protein, BACE (β-site amyloid precursor protein-cleaving enzyme), whereas γ-secretase activity was shown to depend on four components: presenilin, nicastrin, APH-1 (anterior pharynx defective 1) and PEN-2 (presenilin enhancer 2) (Figure). Alternatively, amyloid precursor protein can be proteolytically cleaved by α-secretase, which cleaves it within the Aβ domain. This pathway is non-amyloidogenic (ie, it does not generate the toxic Aβ species[6-8]).

Neurofibrillary lesions: These lesions are the second histopathological hallmark of AD. They are found in cell bodies and apical dendrites as neurofibrillary tangles, in distal dendrites as neuropil threads, and in the abnormal neurites associated with some Aβ plaques (neuritic plaques). The major components of these lesions are abnormal filaments of the microtubule-associated protein tau. In the course of AD, tau becomes abnormally phosphorylated, adopts an altered conformation and is relocalised from axonal to somatodendritic compartments. Phosphorylation tends to dissociate tau from microtubules. As this increases the soluble pool of tau, it might be an important first step in the assembly of tau filaments. Furthermore, microtubules disintegrate in the course of this process, thereby severely compromising the transport machinery of the neurones.[7-9] Evidence is increasing that toxicity is not restricted to the fibrillar species, but that oligomeric forms of tau and Aβ may be even more toxic.

Lewy bodies: In more than 50% of AD cases, neurofibrillary tangles and plaques coexist with a third type of protein deposit, Lewy bodies.[10] The latter are the hallmark lesions of Parkinson's disease, where they are composed of aggregated α-synuclein. In comparison, the Lewy body variant of AD is defined by the presence of all three protein aggregates — Aβ, tau and α-synuclein. These share "amyloid" properties: they have a β-pleated sheet structure and can be stained with dyes such as thioflavin-S.[11] Hence, the term "brain amyloidosis" has been coined.

Tauopathies: Tau-containing lesions are found in about two dozen diseases collectively termed tauopathies, with AD being the most common subtype.[7-9] However, unlike AD, most tauopathies are characterised by the absence of plaques.[12] This has important implications, as an Aβ-directed therapy will likely be ineffective unless it targets common pathogenic mechanisms or common "amyloid" characteristics of the aggregates. In AD, tau aggregates are confined to neurones, but in corticobasal degeneration and progressive supranuclear palsy, they are also abundant in glial cells, such as astrocytes and oligodendrocytes. In Pick's disease, a specific form of frontotemporal dementia, tau aggregates are found in spherical lesions termed Pick's bodies. Further differences are in the tau species found in the aggregates, the degree and sites of tau phosphorylation, and the affected brain areas.[1] Given the pronounced heterogeneity of frontotemporal dementia and high frequency of mixed types, drug screening efforts should not be restricted to Aβ, but should also target tau.

Cleavage pathways for amyloid precursor protein (APP)



APP may be cleaved by membrane-associated α-secretase (a disintegrin and metalloproteinase [ADAM] 10), which cleaves it within the Aβ domain, thus precluding formation of Aβ peptide. This pathway is therefore non-amyloidogenic.

Alternatively, APP may be cleaved through the endosomal–lysosomal pathway, first by β-secretase and then by γ-secretase, generating the Aβ peptide. Mutations found in familial cases of Alzheimer's disease are indicated by asterisks.

Sporadic and familial cases

In the rare familial forms of AD, pathogenic mutations have been identified in both the gene encoding the Aβ precursor (amyloid precursor protein) and in the presenilin genes that encode part of the protease complex involved in Aβ formation[13] (Figure). As carriers of these mutations inevitably develop both plaques and neurofibrillary tangles, this genetic evidence has led to the amyloid cascade hypothesis, which claims that, at least in familial forms of AD, Aβ induces neurofibrillary tangles.

For the more frequent forms of late-onset sporadic AD, two dozen risk-conferring genes have so far been identified, including (very recently) ubiquilin,[14] but only the apolipoprotein E gene has been confirmed unanimously.[15] When sporadic AD is compared with familial AD, the histopathological hallmarks are indistinguishable. This implies that lessons learned from familial AD may also apply to sporadic AD, in particular those derived from animal models expressing familial AD mutant genes.

No mutations have been identified in the tau gene in AD. However, tau mutations have been identified in more than 100 families with familial forms of frontotemporal dementia (FTDP-17), proving that tau dysfunction in itself can lead to neurodegeneration and dementia. ◆