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Alzheimer’s disease: the amyloid hypothesis on trial

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Summary
The pathogenesis of Alzheimer’s disease is complex. The amyloid hypothesis has directed research efforts for many years, but it has recently been questioned after failed drug trials. Here, we review the evidence for and against and suggest that it might be premature to abandon the amyloid hypothesis

Declaration of interest
None.

The amyloid hypothesis of Alzheimer’s disease proposes that deposition of beta-amyloid (Ab) protein is central to the pathogenesis of the disorder.1 It has been the foundation of efforts to understand the disease for almost 25 years. However, recently its validity has been called into question after the failure of Ab-targeting therapies in clinical trials. Some have even suggested that the causal link between Ab and Alzheimer’s disease has been refuted.2

The pathology of Alzheimer’s disease

The classical histological features of Alzheimer’s disease are a triad of Ab plaques, neurofibrillary tangles and neuronal cell loss.3 The first of these are insoluble extracellular plaques consisting of Ab, which accumulates in very high levels in the brains of those with Alzheimer’s disease. Ab is derived from a larger molecule, amyloid precursor protein (APP). APP is a trans-membrane protein, with a long extracellular N-terminal and a shorter intracellular C-terminal. The Ab sequence consists of some of the extracellular portion and part of the trans-membrane domain, and is 39–42 amino acids in length. The protein has a b-pleated sheet structure, and demonstrates Congo red birefringence and resistance to proteolysis.4 In Alzheimer’s disease, Ab is deposited in abundant extracellular plaques typically composed of straight fibrils, 6–10 nm in diameter. These structures are also found in normal ageing but in less profusion and are sometimes referred to as senile plaques. They are associated with dystrophic neurites and changes in microglia and astrocytes.3 Non-fibrillar, diffuse Ab deposits, which are not associated with dystrophic neurites or reactive glial cells, are also found in Alzheimer’s disease and these may represent an early stage plaque formation. In Alzheimer’s disease these diffuse plaques are found throughout the central nervous system, whereas typical Ab plaques are not present in regions such as the spinal cord and cerebellum.4

The second pathological structure found in Alzheimer’s disease is the neurofibrillary tangle. These consist of dystrophic neurites containing paired helical filaments, 10 nm in diameter. These paired helical filaments consist of a phosphorylated microtubule-associated protein, tau (MAPT).3 In the 1980s there was much debate as to which one of these is the primary driver of Alzheimer’s disease pathogenesis. The issue seemed to be resolved with the advent of a new generation of molecular genetic studies.5

Genetics

Early molecular genetic studies of Alzheimer’s disease focused on rare families where the disorder occurs exceptionally early and follows an autosomal dominant mode of inheritance. It was discovered that so-called familial Alzheimer’s disease is caused by mutations either in the APP gene itself, or in presenilin 1 and 2 (PS1 and PS2) that are involved in cleaving Ab from APP.5 In addition, Alzheimer's disease frequently affects those with trisomy 21, who have a triplication of the APP gene.5 On these grounds, Hardy & Allsop4 postulated that APP mismetabolism and Ab deposition are the primary events in the disease process with tau phosphorylation and neurofibrillary tangle formation occurring downstream. This became known as the amyloid hypothesis. It later transpired that the familial Alzheimer's disease genes increase levels of 42 amino acid Ab (Ab42) relative to the shorter 40 amino acid protein, and this form of Ab aggregates more readily into plaques.6

Biomarkers

The hypothesis has received further support from widely replicated biomarker studies. Brain Ab deposition in Alzheimer's disease can be demonstrated in vivo using biomarkers such as cerebrospinal fluid (CSF) Ab42 and Ab positron emission tomography (PET) imaging.7 Clinical diagnoses of Alzheimer's disease and Ab pathology at autopsy correlate with low concentrations of CSF Ab42. Most patients with a diagnosis of Alzheimer's have increased retention of radioligands for Ab on PET. Moreover, low CSF Ab and positive Ab PET show nearly 100% concordance.7

Thus, a substantial body of evidence appears to support a causative, pathogenic link between Ab and Alzheimer's disease. However, there are a few pieces of the Alzheimer's jigsaw that do not quite fit.

Challenges to the amyloid hypothesis

Alzheimer's is not an all-or-none phenomenon even at the neuro-pathological level. Moreover, autopsy studies find sufficient numbers of Ab plaques and neurofibrillary tangles to meet criteria for a diagnosis of Alzheimer's disease in around a third of cognitively intact elderly people.8 This is corroborated by biomarker studies, which suggest that 20–40% of elderly people without cognitive impairment show significant brain Ab load, either on Ab PET or CSF Ab42 concentrations.8

The topographic distribution of Ab plaques differs from neurofibrillary tangle deposition and neurodegenerative changes. In early Alzheimer's disease, neural loss is predominantly in the hippocampus and entorhinal cortex, whereas plaques are first found in frontal regions, basal ganglia or elsewhere.7,9 Clinical symptoms are more closely associated with neurofibrillary tangles than Ab burden. However, cerebral atrophy, representing neuron and synapse loss, corresponds best to cognitive impairment.10

How distant Ab plaques might induce neurofibrillary tangles or damage neurons is unclear. It has been proposed that soluble oligomers of Ab could be neurotoxic. Although soluble oligomers cannot be seen in vivo or post-mortem, they have been found to interfere with postsynaptic potentiation in tissue culture studies. However, the concentration of Ab oligomers shown to have this effect is greater than usual physiological levels.11 Another suggestion is that Ab plaques could act as a 'reservoir' eluting soluble Ab, but Ab has a strong tendency to polymerise and fix fragments to plaques, which makes this less likely.11 Furthermore, many animal models based on APP and PS1 mutations have not shown progression to synaptic loss, neurofibrillary tangle formation and neurodegeneration.6

Critics of the amyloid hypothesis also point out that familial Alzheimer's disease, where the aetiological link with APP is strong, is rare and might be an atypical form of the disorder. They point to recent genome-wide association studies (GWAS), which have implicated many novel genes as containing risk factors for typical Alzheimer's disease but not APP or its metabolising enzymes. In defence of the amyloid hypothesis, GWAS only assess common genetic variation and failure to find association does not exclude an important role for a protein in disease. Moreover, some of the genes implicated by GWAS may be involved in Ab processing. For example, CLU encodes clusterin, which binds soluble Ab in animal models, forming complexes that can cross the blood–brain barrier, and PICALM encodes phosphatidylinositol binding clathrin assembly protein, which has been postulated to increase Alzheimer's disease risk through APP processing via endocytic pathways, resulting in changes in Ab levels.12

Clinical trials

The biggest challenge to the amyloid hypothesis has come from the failure of phase III trials of anti-Ab therapies2 despite promising results in animal models.6 Critics point to notable therapeutic failures, such as semagacestat, an inhibitor of gamma (g)-secretase, an enzyme responsible for the cleavage of APP to produce pathogenic Ab.13 Participants in the active treatment arm had poorer cognitive out-comes, and the trial was terminated. The trial of immunisation with aggregated human Ab, AN1792, was halted when some participants developed autoimmune encephalopathy, and there was no effect on disease progression.14

This raises a key question. Does the failure of these trials effectively refute the amyloid hypothesis? There are two general reasons why this conclusion might be premature. First, there could have been insufficient target engagement. Second, the drugs may have been administered too late in the disease process.

In an analysis of six programmes testing anti-Ab therapies, Karran & Hardy15 identified various deficiencies. This suggested that the failure of phase III trials of anti-Ab agents might be because of problems with pharmacokinetics, dosing, outcome measures etc., rather than shortcomings of the amyloid hypothesis.15 An analysis by pharmaceutical industry investigators16 reached a similar verdict: negative trials did not demonstrate sufficient target engagement to assess whether reducing Ab load could modify the course of Alzheimer's disease.

Early research assumed that abnormal deposition of Ab is a proximal cause of neurodegeneration in Alzheimer's disease. An alternative model is that production of Ab at abnormal levels begins much earlier in life, is integral to the inception of the disease process, but the subsequent pathological cascade becomes autonomous. If this were true, anti-Ab therapies would only be effective if administered early in the disease process. Support for this view comes from biomarker studies showing a clear sequence of abnormalities as the disease progresses.10 The earliest markers of brain Ab deposition are reductions in CSF Ab42 followed by increased Ab PET tracer uptake. These changes occur in the 'preclinical' phase17 and, by the time cognitive impairment is clinically detected, Ab markers have plateaued. Subsequently, neuronal injury and neurodegeneration predominate. These are shown by increased CSF tau and cerebral atrophy on structural magnetic resonance imaging. Decreased fluorodeoxyglucose uptake on PET indicates accompanying synaptic dysfunction. These markers, which become abnormal later in the disease, correlate closely with clinical symptoms7 (Fig. 1).

The failed therapeutic trials may also support this chronological pattern. For example, the AN1792 immunisation,14 which did not improve cognition and had minimal effect on neural loss, gliosis and tau accumulation, did reverse Ab deposition. The number of patients followed up, however, was small. This is consistent with the view that, in its later stages, the pathogenic process is not dependent on Ab deposition, even if it is triggered by it. This means that the timing of any intervention in the Alzheimer's pathological process is crucial. It also makes Ab levels an equivocal proxy end-point for clinical trials at least in the later stages of the process.18

Among the strongest recent evidence that reducing Ab cleavage may protect against Alzheimer’s disease is the discovery of a rare mutation in the APP gene that is associated with decreased Ab synthesis and which protects against Alzheimer’s disease and cognitive decline in elderly people.19 Further support for the amyloid hypothesis has come from recent work using human neural stem-cell-derived cultures in a three-dimensional system to model the effects of familial Alzheimer’s disease mutations. They deposited Ab and aggregates of phosphorylated tau. Further-more, inhibition of Ab generation with b-or g-secretase inhibitors decreased both Ab and tau.19

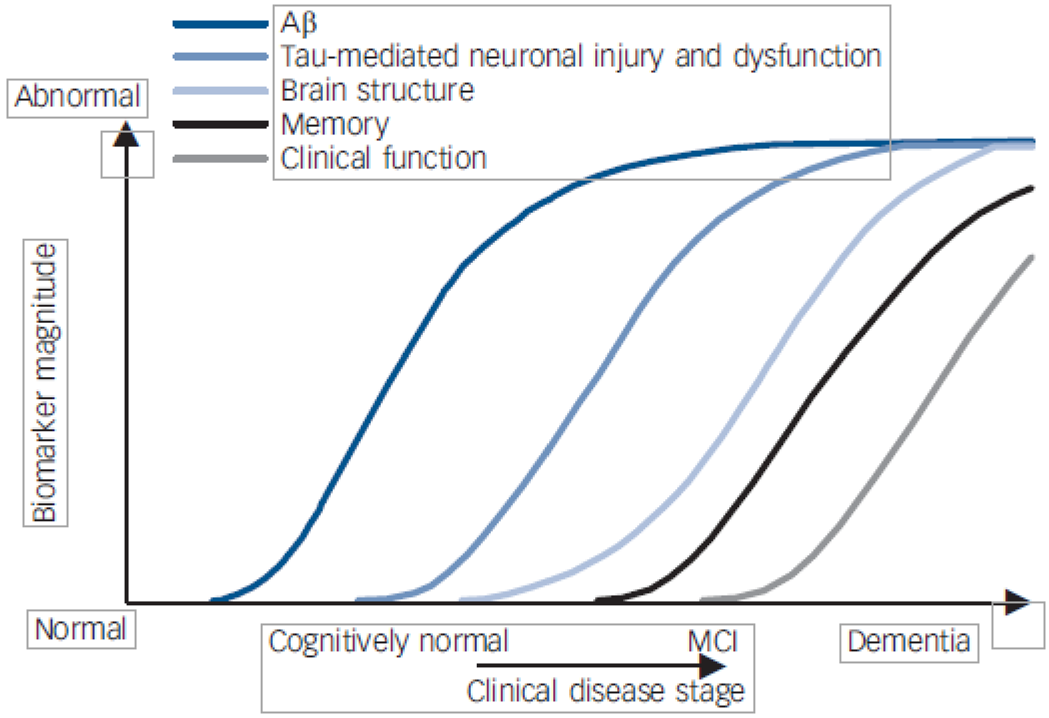

Fig. 1 Biomarkers of the Alzheimer’s pathological cascade

Beta-amyloid (Ab) is indicated by low cerebrospinal fluid (CSF) Ab42 or positron emission tomography (PET) Ab imaging. Tau neuronal injury and dysfunction is shown by CSF tau or fluorodeoxyglucose-PET. Cerebral atrophy is measured with structural magnetic resonance imaging. MCI, mild cognitive impairment. Reprinted with permission from Elsevier Limited. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade. Lancet Neurol 2010; 9: 119–28.

Implications

The emerging evidence suggests that Ab deposition occurs early in Alzheimer’s disease, and the correct timing of interventions may turn out to be crucial. Identifying asymptomatic individuals who have Ab-related neurodegeneration will be important, as not all patients currently selected for Alzheimer’s disease drug trials have Ab-positive PET imaging.20 Trials of anti-Ab therapy in cognitively normal elderly people with positive Ab biomarkers and younger, asymptomatic, individuals who carry a familial Alzheimer’s disease mutation are underway21,22 and, if successful, will support the need for anti-Ab therapies to be given before cognitive decline has become established.

There is increasing interest in the possibility that the key to treating the disorder may be to identify those at risk long before they develop symptoms, as hyperlipidaemia and hypertension are treated years before myocardial or cerebral infarction. This will require the right anti-Ab drugs to be given to the right patients, those at high risk and at the right time, before irreversible changes have taken place.10 This will require much further research. Although biomarkers can detect asymptomatic amyloidosis, large longitudinal studies will be needed to investigate their usefulness as predictive tests.11 Geneticprofilingmayalsohavearole,usingrisk profile scores based on panels of single nucleotide polymorphisms that are associated with increased risk.12

Despite two decades of intensive work, the amyloid hypothesis has not led to the hoped for therapeutic advances. This has caused some to question its validity and to ask whether efforts aimed at reducing Ab synthesis are ever likely to be successful. The finding of a mutation in APP that protects against Alzheimer's disease and reduces the production of Ab suggests that it may be premature to write off the amyloid hypothesis. Moreover, the negative results of therapeutic trials should be interpreted in the light of evidence that Ab deposition occurs early in the preclinical phase of the illness. The emerging paradigm of targeting treatments at asymptomatic high-risk individuals remains untested, but if this gains support, it will signal a sea change in the way in which Alzheimer's disease is treated with a move from tertiary to secondary prevention.

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