The Future of Alzheimer's

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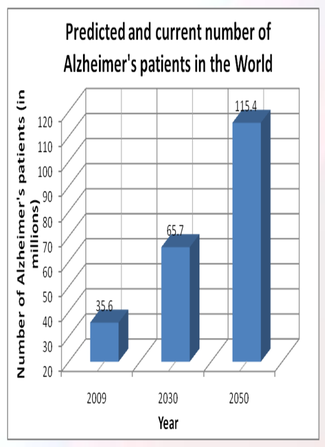
Introduction

Alzheimer's disease (AD) is the most common form of dementia but despite its prevalence the disease mechanisms are poorly understood and treatments far from effective[1].

Since more than 1 million people are expected to be affected by 2050 in the UK[1], this debilitating disease is likely to play a large part in our future careers (Graph 1).



Graph 1. The current and predicted number of Alzheimer's patients.

What happens in Alzheimer's?

Physiological changes in Alzheimer's

Typically, AD has the following characteristics:

1. Atrophy in the neocortex and hippocampus
2. Decreased matter in the gyri, so enlarged sulci
3. **β-Amyloid (Aβ) plaques**
4. **Neurofibrillary tangles**

3 and 4 above are subject to intensive investigation and are discussed in more detail below.

Amyloid plaques

Amyloid plaques form when **amyloid precursor protein** (APP) is cleaved by a particular pathway (there are two)[2]. The enzymes involved in this pathway are (see Fig. 2)[3]:

1. β-secretase
2. γ-secretase

These enzymes produce oligomers of Aβ. If these consist of **Aβ-42** tiny fibrils form and aggregate to produce the amyloid plaques.

Neurofibrillary tangles

These originate from a protein called **tau**, which is important in microtubule assembly. Due to enzyme over-activity, tau is hyperphosphorylated, which is insoluble and aggregates to form **tangles** (see Fig. 1)[3].

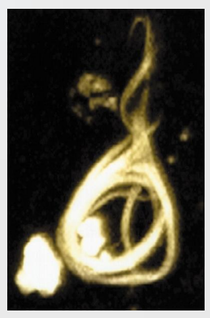


Figure 1. A neurofibrillary tangle.

The genetic causes of Alzheimer's

Chromosomal anomalies/mutations causing AD have been found on chromosomes 21, 14 and 1. These errors are primarily in the **APP gene** (c21) and usually increase **Aβ-42** levels, leading to Aβ plaque formation[2].

However, the majority of AD cases result from old-age dementia rather than chromosomal anomalies /mutations. Several '**vulnerability genes**' have been identified as risk factors for this type of Alzheimer's[2].

The main 'vulnerability' gene is the ***APOE*** gene. Three common alleles of this gene exist. *APOE-4* is the allele associated with AD. It is thought to increase the deposition of Aβ, and so result in plaque formation[3].

How is Alzheimer's diagnosed?

Diagnosis of AD is based on:

1. Progressive impairment of memory
2. Decline in one other cognitive domain
3. Changes in personality

Diagnostic stages:

1. Medical history
2. Physical examination
3. Neuropsychological testing
4. **Medical Imaging**

Current imaging techniques:

SPECT: This measures blood flow in the brain. In patients with Alzheimer's it shows bilateral hypometabolism[3].

PET Scans: Use of FDG (flurodeoxyglucose) PET scan can diagnose presymptomatic AD approximately two years before full manifestation (see Fig. 3)[3].

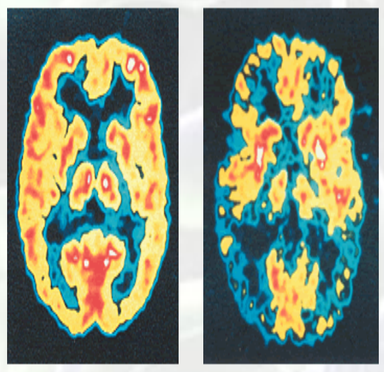


Figure 3. Comparison of a PET scan of a control (left) and an AD patient (right).

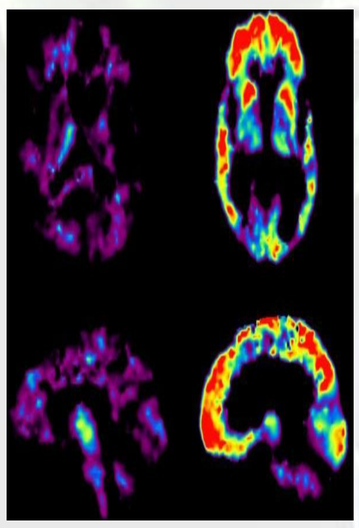


Figure 4. Comparison of a PET (with PIB) scan of a control (left) and an AD patient (right). This shows there is more Aβ in the AD patient than the control.

Neurotransmitter (NT) scanning: This is used to assess release of NT's *in vivo* when studying nicotinic acetyl choline receptors[3].

Future techniques:

Amyloid Imaging: Used for detection of Aβ in AD. A new agent (PIB) is used in conjunction with a PET scan. This binds to Aβ and hence can measure amounts of Aβ (Fig. 4)[3].

DTI- Diffusion Tensor imaging: This measures the random motion of water within the brain and detects changes in the white matter of the brain. It has been shown that the health of the brain is better predicted by a DTI scan compared to a traditional MRI scan[3].

What interventions are available?

The pharmacological approach

Current treatments only address the symptoms rather than causes of AD, demonstrating our poor understanding of the disease. Currently approved drugs include:

1. **Donepezil**
2. **Galantamine**
3. **Rivastigmine**
4. **Tacrine**

These are acetyl cholinesterase inhibitors which improve cognitive function within 6-18 months.

5. **Memantine** — *A methyl-d-aspartate antagonist - reduces neuronal excitotoxicity.*

Systematic reviews and economic evaluation studies highlight the high cost and limited effect of these drugs. As a result NICE guidelines do not recommend memantine for moderate to severe AD patients.

Much hope is being placed on new research addressing the causative mechanisms of the disease.

Targeting β-amyloid protein

New research aimed at **the APP pathway** tries to inhibit enzymes responsible for plaque formation. The enzymes involved are **β-** and **γ-secretases**. Both β inhibitors (e.g. BACE, aspartic acid protease inhibitors) and γ inhibitors (e.g. LY4501B9 from Eli Lilly) are in phase three clinical trials.

It has also been suggested that **antibodies** (via passive or active immunity) can be used to clear the Aβ from the CNS, thus reducing plaque formation.

Targeting neurofibrillary tangles

Another area of research is aiming to prevent tau aggregation, thus reducing tangle formation. Methylene blue works in this way and has progressed to phase 3 clinical trials, and has thus far shown promising results.

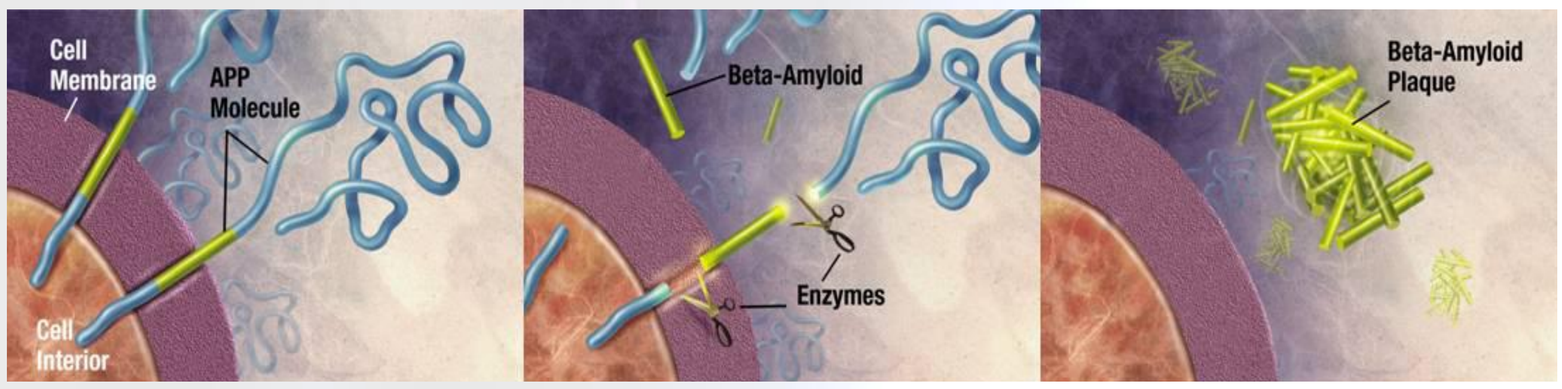


Figure 2. The formation of amyloid plaques. The two enzymes depicted are β-secretase and γ-secretase.

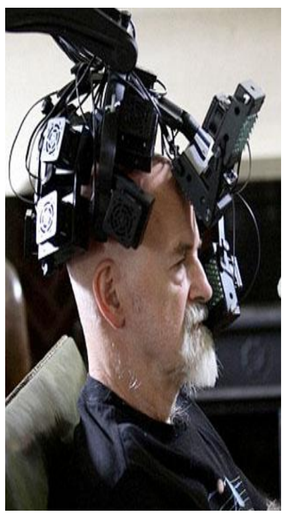


Figure 5. The equipment used to fire infrared light into the brain to stimulate of brain cell repair.

Other forms of treatment

Infrared light: Firing **infrared** light into the brain is thought to stimulate repair of brain cells (see Fig 5). This therefore slows the progression of Alzheimer's and is currently undergoing clinical trials.

Leptin: This hormone inhibits hunger and counteracts neuropeptide Y to prevent over-eating. High levels have been shown to **reduce extracellular Aβ and tau phosphorylation**.

Cognitive stimulation: This aims to **stimulate** and **engage** patients, thereby helping restore memory function and sense of identity.

Conclusion

Knowledge of AD is rapidly evolving due to new imaging technology and innovative pharmacological interventions.

Current focus on the amyloid hypothesis needs further research in order to be accepted by the scientific community. The high profile of the infrared 'helmet' in the media offers hope for maintaining cognitive skills.

Many avenues are being explored but as yet none have offered the 'wonder cure' for AD.

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