Alzheimer's disease

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Alzheimer's disease is the most common cause of dementia. Research advances have enabled detailed understanding of the molecular pathogenesis of the hallmarks of the disease—ie, plaques, composed of amyloid β (Aβ), and tangles, composed of hyperphosphorylated tau. However, as our knowledge increases so does our appreciation for the pathogenic complexity of the disorder. Familial Alzheimer's disease is a very rare autosomal dominant disease with early onset, caused by mutations in the amyloid precursor protein and presenilin genes, both linked to Aβ metabolism. By contrast with familial disease, sporadic Alzheimer's disease is very common with more than 15 million people affected worldwide. The cause of the sporadic form of the disease is unknown, probably because the disease is heterogeneous, caused by ageing in concert with a complex interaction of both genetic and environmental risk factors. This seminar reviews the key aspects of the disease, including epidemiology, genetics, pathogenesis, diagnosis, and treatment, as well as recent developments and controversies.

Lancet 2006; 368: 387–403

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100 years ago, Alois Alzheimer gave a lecture at a congress in Tübingen, Germany, on the first case of the disease that Kraepelin some years later named Alzheimer's disease.[1] In this single case, Alzheimer described typical clinical characteristics with memory disturbances and instrumental signs, and the neuropathological picture with miliary bodies (plaques) and dense bundles of fibrils (tangles), which we today know are the hallmarks of the disease. Here, we review the epidemiology, genetics, pathogenesis, diagnosis, and treatment of the disease. We also cover the latest discoveries on the molecular pathogenesis and the implications for the development both of new drug candidates with potential disease-modifying effects and of new methods for early diagnosis, taking into account existing controversies.

Epidemiology and risk factors

Alzheimer's disease is the most common form of dementia, accounting for 50–60% of all cases. The prevalence of dementia is below 1% in individuals aged 60–64 years, but shows an almost exponential increase with age, so that in people aged 85 years or older the prevalence is between 24% and 33% in the Western world.[2] Representative data from developing countries are sparse, but about 60% of patients with dementia are estimated to live in this part of the world. Alzheimer's disease is very common and thus is a major public-health problem. In 2001, more than 24 million people had dementia, a number that is expected to double every 20 years up to 81 million in 2040 because of the anticipated increase in life expectancy.[2]

Besides ageing, which is the most obvious risk factor for the disease, epidemiological studies have suggested several tentative associations. Some can be linked to a decreased reserve capacity of the brain, including reduced brain size, low educational and occupational attainment, low mental ability in early life, and reduced mental and physical activity during late life.[3,4] The brain reserve capacity is determined by the number of neurons and their synaptic and dendritic arborisation together with lifestyle-related cognitive strategies. A low reserve capacity has been linked with early presentation of some pathological changes of the disease.[3] Moreover, several epidemiological studies have shown that head injury could be a risk factor.[5] Whether brain trauma initiates the pathogenic cascade leading to plaque and tangle formation or whether it simply reduces the brain reserve capacity is unclear.

Other risk factors are associated with vascular disease, including hypercholesterolaemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes.[3] Whether these are true causal risk factors for Alzheimer's disease, driving the pathogenic processes resulting in plaque and tangle formation, or whether they induce cerebrovascular pathology, which adds to clinically silent disease pathology thus exceeding the threshold for dementia, needs to be established. Some evidence suggests that dietary intake of homocysteine-related vitamins (vitamin B12 and folate); antioxidants, such as vitamin C and E; unsaturated fatty acids; and also moderate alcohol intake, especially wine, could reduce the risk of Alzheimer's disease,[6] but data so far are not conclusive to enable any general dietary recommendations to be made. Although environmental factors might increase the risk of sporadic Alzheimer's disease, this form of the disease has been shown to have a significant genetic background. A large population-based twin study showed that the extent of heritability for the sporadic disease is almost 80%.[7]

Search strategy and selection criteria

We searched PubMed for English language articles on Alzheimer's disease using the keyword "Alzheimer" alone or together with other keywords including: "amyloid", "CSF", "CT", "diagnosis", "epidemiology", "genetic", "imaging", "MRI", "PET", "risk factors", "tau", "therapy", "transgenic", "treatment", and several other keywords relevant to every section. We largely selected publications in the past 5 years, but did not exclude important older publications. Selection criteria also included a judgment on the novelty of studies and their relevance for the well-informed general physician.

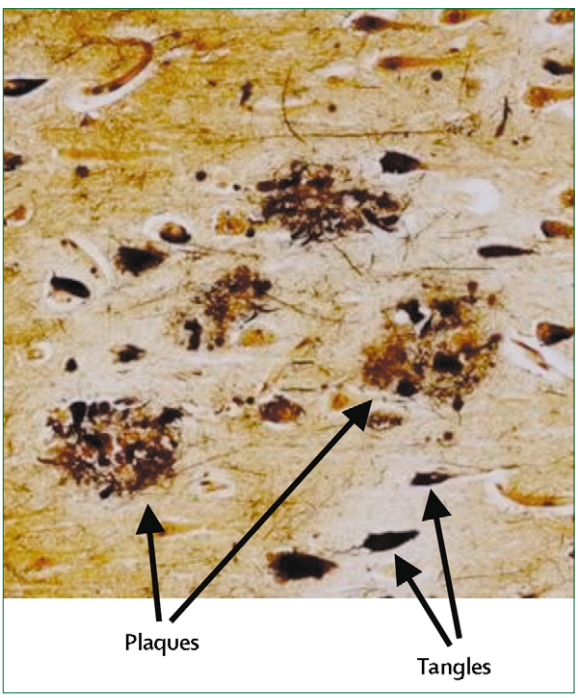

Figure 1: **Plaques and tangles in the cerebral cortex in Alzheimer's disease**
Plaques are extracellular deposits of Aβ surrounded by dystrophic neurites, reactive astrocytes, and microglia, whereas tangles are intracellular aggregates composed of a hyperphosphorylated form of the microtubule-associated protein tau.

Genetics

For **an overview of published genetic association studies on Alzheimer's disease** see the Alzgene database at http://www.alzgene.org

From a genetic standpoint, Alzheimer's disease is a heterogeneous disorder with both familial and sporadic forms.

Genes implicated in familial disease

Familial Alzheimer's disease is an autosomal dominant disorder with onset before age 65 years. The first mutation causing the familial form of the disease was identified in the amyloid precursor protein (*APP*) gene on chromosome 21.[8] When investigating other families with the familial disease, several additional *APP* mutations were found. However, these mutations explain only a few familial cases. Instead, mutations in the highly homologous presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes account for most cases of familial disease.[9,10] However, the familial form of the disease is rare, with a prevalence below 0·1%.[11]

Genes implicated in sporadic disease

In 1993, two groups independently reported an association between the apolipoprotein E (*APOE*) ε4 allele and Alzheimer's disease.[12,13] Meta-analysis shows that the *APOE* ε4 allele increases the risk of the disease by three times in heterozygotes and by 15 times in homozygotes.[14] The *APOE* ε4 allele operates mainly by modifying age of onset,[15] with each allele copy lowering the age at onset by almost 10 years.[12]

The molecular mechanism for the disease-promoting effect has been difficult to pinpoint. ApoE acts as a cholesterol transporter in the brain with ApoE4 being less efficient than the other variants in reuse of membrane lipids and neuronal repair.[16] On the other hand, ApoE is essential for amyloid β (Aβ) deposition, promoting Aβ fibrillisation and plaque formation[17] possibly by acting as a pathological chaperone. The gene-dose dependent reduction in CSF Aβ42 could be associated with this process.[18]

The *APOE* ε4 allele has been calculated to account for most of the genetic risk in sporadic Alzheimer's disease.[19] Thus, the contribution of other candidate genes is probably minor. Indeed, several studies have reported weak associations with different candidate genes, but none has been verified with certainty.[20] A possible explanation for this difficulty could be that the sporadic form of the disease is not a homogeneous disease entity, and that several susceptibility genes act in concert, each conferring only a minor increase in risk, in a complex interaction with environmental factors.

Pathogenesis

At the microscopic level, the characteristic lesions in Alzheimer's disease are senile or neuritic plaques and neurofibrillary tangles (figure 1) in the medial temporal lobe structures and cortical areas of the brain, together with a degeneration of the neurons and synapses. Several pathogenic mechanisms that underlie these changes have been studied, including Aβ aggregation and deposition with plaque development, tau hyperphosphorylation with tangle formation, neurovascular dysfunction, and other mechanisms such as cell-cycle abnormalities, inflammatory processes, oxidative stress, and mitochondrial dysfunction.

The finding of a correlation between plaque counts and dementia severity put great focus on the involvement of plaques in the pathogenesis of the disease.[21] Because of their insolubility, attempts to identify the protein composition of plaques were fruitless until the mid-1980s when researchers succeeded in purifying plaque cores and identifying the aminoacid sequence of Aβ, the major plaque component.[22] This finding paved the way for the cloning of the *APP* gene.[23]

Initially, Aβ found in senile plaques was thought to be an abnormal protein. Therefore, an important finding was that Aβ is produced constitutively during normal cell metabolism.[24] This finding initiated a search for the two hypothetical enzymes excising Aβ from APP, which were designated β-secretase and γ-secretase (figure 2). γ-secretase is an intramembranous protease complex, consisting of four components: presenilin, nicastrin, PEN-2, and APH-1, with presenilin constituting the active site.[25] Most β-secretase activity originates from an integral membrane aspartyl protease called β-site APP-cleaving enzyme 1 (BACE1).[26] In the non-amyloidogenic pathway (figure 2), two proteases with α-secretase activity

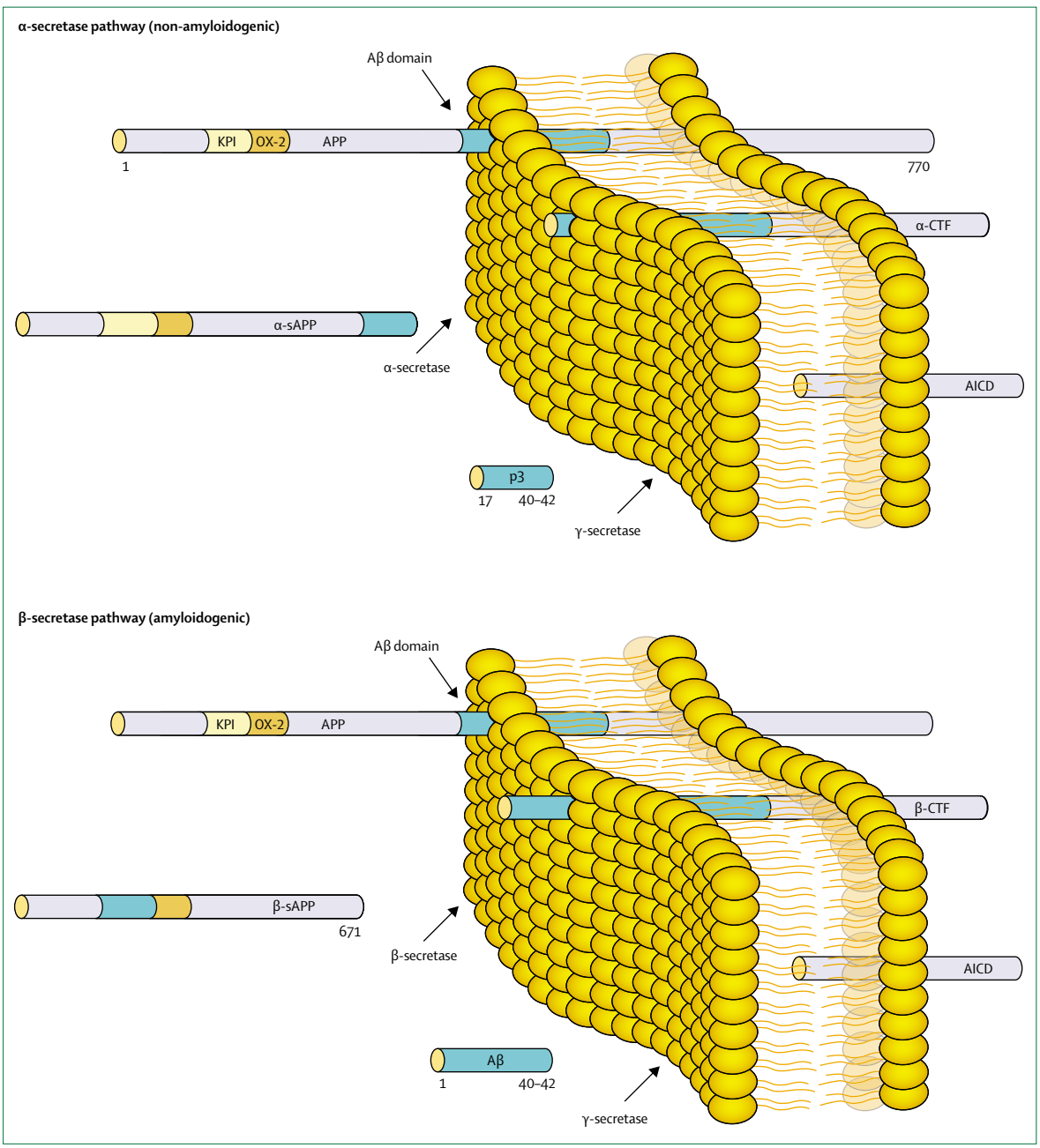

Figure 2: **Metabolism of amyloid precursor protein (APP) with amyloid β (Aβ) generation**
APP is a transmembrane protein with a large N-terminal extracellular tail. The largest isoform of APP (APP770) is shown, containing the Kunitz-type protease inhibitor (KPI) domain (which is lacking on the APP695 isoform) and the OX-2 antigen domain (which is lacking on both the APP695 and the APP751 isoforms). The Aβ domain is partly embedded in the plasma membrane and includes the 28 residues just outside the membrane and the first 12–14 residues in the transmembrane domain. APP can be processed along two main pathways. In the α-secretase pathway, α-secretase cleaves APP within the Aβ domain, releasing the large soluble APP fragment (α-sAPP). The remaining C-terminal fragment (CTF), α-CTF, or C83, is cleaved by the γ-secretase complex releasing the short p3 peptide. The remaining APP intracellular domain (AICD) is metabolised in the cytoplasm. Since APP cleavage by α-secretase is within the Aβ domain this precludes Aβ generation. In the β-secretase pathway, β-secretase cleaves APP just before the Aβ domain, releasing soluble βsAPP. The remaining CTF, β-CTF, or C99 is cleaved by the γ-secretase complex releasing the free 40 or 42 aminoacid Aβ peptide. The remaining AICD is metabolised in the cytoplasm.

belonging to the ADAM family of disintegrin and metalloproteinases have been identified.[27,28]

Under normal conditions, brain Aβ is degraded by the peptidases insulin-degrading enzyme, neprilysin, and by endothelin-converting enzyme.[29] Aβ is also cleared from the brain in a process balanced by the efflux, mediated by low-density lipoprotein receptor-related protein, and the influx, mediated by the receptor

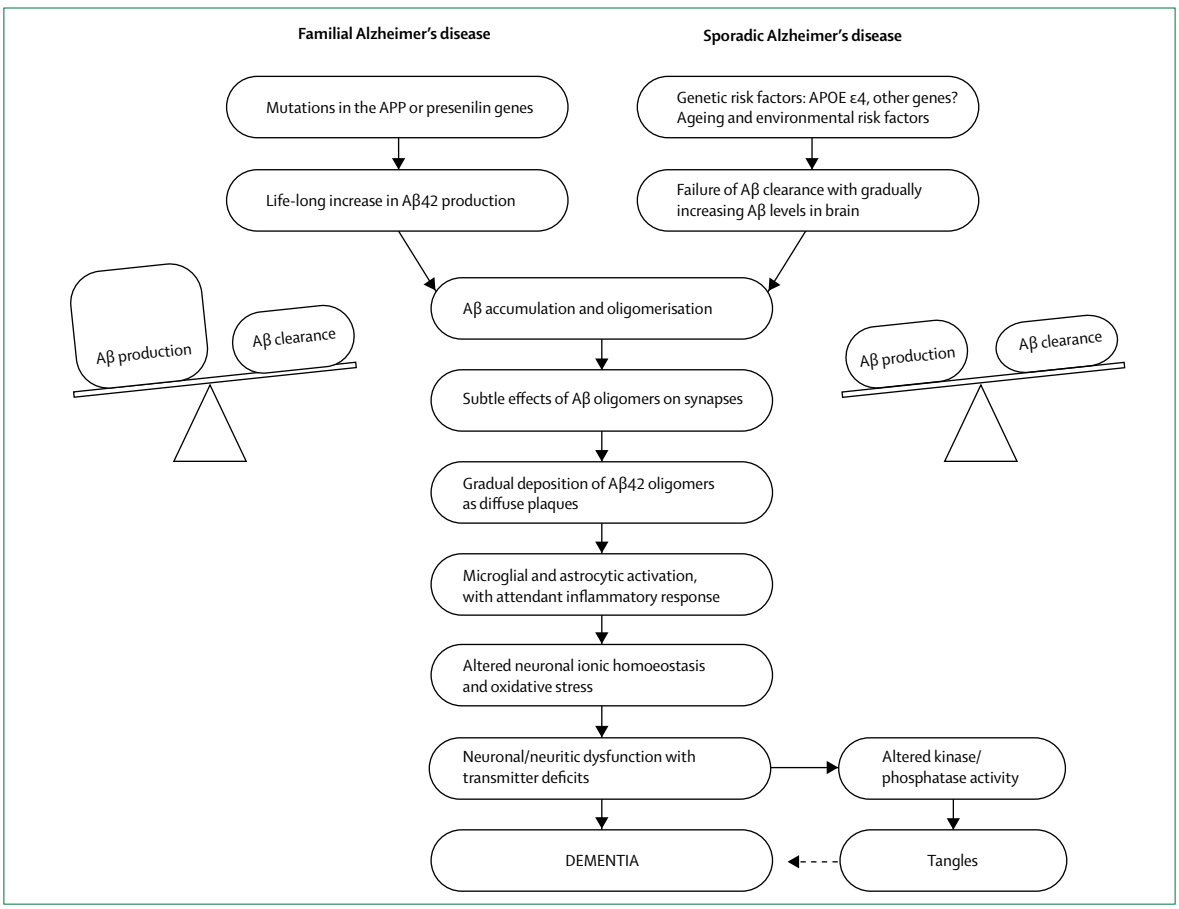

Figure 3: **Amyloid cascade hypothesis**
According to this hypothesis, the central event in the disease pathogenesis is an imbalance between Aβ production and clearance, with increased Aβ production in familial disease and decreased Aβ clearance in sporadic disease. Aβ oligomers could directly inhibit hippocampal long-term potentiation and impair synaptic function, in addition to the inflammatory and oxidative stress caused by aggregated and deposited Aβ. These processes impair neuronal and synaptic function with resulting neurotransmitter deficits and cognitive symptoms. Tau pathology with tangle formation is regarded as a downstream event, but could contribute to neuronal dysfunction and cognitive symptoms.[31]

for advanced glycation end products, of Aβ across the blood–brain barrier.[30] There is no evidence for any disturbances in these proteolytic enzymes or transport mechanisms in Alzheimer's disease.

The central hypothesis for the cause of Alzheimer's disease is the amyloid cascade hypothesis (figure 3), which states that an imbalance between the production and clearance of Aβ in the brain is the initiating event, ultimately leading to neuronal degeneration and dementia.[31] Support for this hypothesis includes the finding that the mutations implicated in the familial disease are present in the genes for both the substrate (APP) and the key enzyme (presenilin) for Aβ generation. Most *APP* mutations also cluster around the secretase sites, and both the *APP* and presenilin mutations increase Aβ42 production. Furthermore, the knowledge that people with Down's syndrome, who possess an extra *APP* gene, develop Aβ plaques early in life, and the recent finding of a duplication of the *APP* locus in families with familial Alzheimer's disease,[32] lent support to the notion that life-long APP overexpression triggers Aβ deposition.

Soluble Aβ is thought to undergo a conformational change to high β-sheet content, rendering it prone to aggregate into soluble oligomers and larger insoluble fibrils in plaques (figure 3). In this process, the fibrillogenic Aβ42 isoform triggers the misfolding of other Aβ species.[33] Initially, only Aβ deposited in plaques was assumed to be neurotoxic, but findings suggest that soluble Aβ oligomers might be the culprits, inhibiting hippocampal long-term potentiation and disrupting synaptic plasticity.[34] One study suggested that Aβ oligomers composed of 12 Aβ peptides are related to memory disturbances in Alzheimer's disease transgenic mice, although no data for sporadic disease were presented.[35]

Almost in parallel with the identification of Aβ in plaques, tangles were shown to be composed of abnormally hyperphosphorylated tau protein.[36,37] Tau is a normal axonal protein that binds to microtubules through its

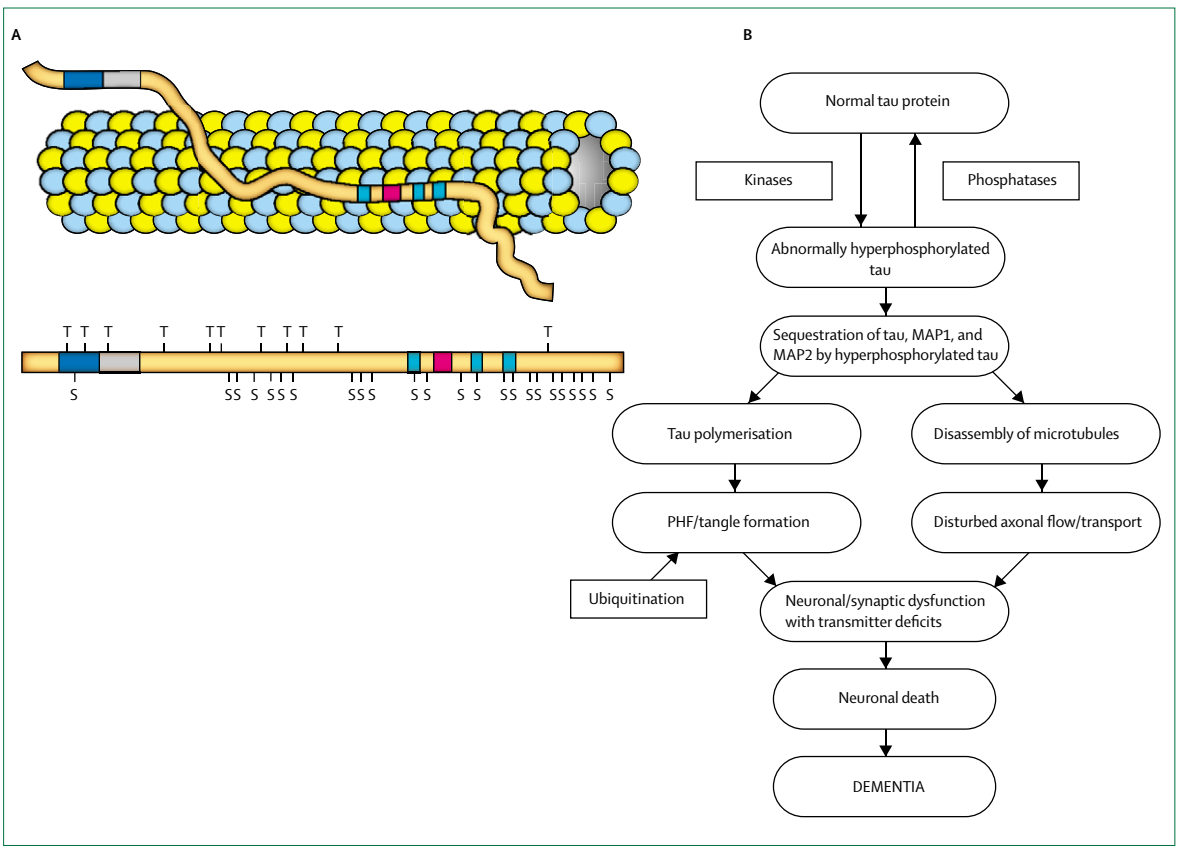

***Figure 4*: Tau protein in Alzheimer's disease**

A: Schematic drawing of tau protein bound to a microtubule through its microtubule-binding domains. The largest of the six tau isoforms is shown, containing four microtubule-binding domains and exons 2 and 3 spliced in. Below is a schematic drawing of hyperphosphorylated tau with phosphorylation sites, either threonine (T) or serine (S). B: Flow chart of tau hyperphosphorylation and tangle formation. Tau phosphorylation is regulated by the balance between multiple kinases and phosphates. Hyperphosphorylated tau sequesters normal tau and other microtubule-associated proteins causing disassembly of microtubules and disturbed axonal transport. Hyperphosphorylated tau also becomes prone to aggregation into insoluble fibrils (paired helical filaments; PHF) and larger aggregates in tangles. Both the loss of microtubule stabilisation and the tangle formation compromise neuronal and synaptic function. Tau in tangles becomes ubiquitinated for non-lysosomal degradation, but this process is inefficient, and tangles may finally choke affected neurons to death.[38]

microtubule-binding domains, thereby promoting microtubule assembly and stability. Tau phosphorylation is regulated by the balance between multiple kinases (eg, GSK-3β and CDK5) and phosphates (eg, PP-1 and PP-2A).[38] Tau hyperphosphorylation in Alzheimer's disease starts intracellularly and leads to sequestration of normal tau and other microtubule-associated proteins, which causes disassembly of microtubules and thus impaired axonal transport, compromising neuronal and synaptic function (figure 4).[38] Tau also becomes prone to aggregation into insoluble fibrils in tangles, further compromising neuronal function. Tau pathology starts early in the disease process in neurons in the transentorhinal region, spreads to the hippocampus and amygdala, and later to the neocortical association areas.[39] Whether tau hyperphosphorylation and tangle formation are a cause or consequence of Alzheimer's disease is unknown.

Some lines of evidence suggest that there may be converging pathogenic mechanisms between cerebrovascular and Aβ plaque pathology. Several studies show comorbidity of cerebrovascular disease and Alzheimer's disease, and also abnormalities in the brain microvascular system.[3,40] The neurovascular hypothesis suggests that dysfunctional blood vessels could contribute to cognitive dysfunction by impairing delivery of nutrients to neurons and by reducing Aβ clearance from the brain.[41] Such cerebrovascular alterations could be initiated by down-regulation of the vascular differentiation gene *MEOX2*, with resulting loss of cerebral microvessels and reduced cerebral blood flow and Aβ efflux from the brain.[42] Additionally, a polymorphism in the vascular endothelial growth factor (*VEGF*) gene might be associated with the sporadic disease.[43] Both human and experimental studies show that cerebrovascular pathology with ischaemia results in upregulation of APP expression followed by Aβ deposition.[44,45] However, other researchers argue that coexisting vascular pathology could occur independently of the disease process and simply increase the probability of dementia in patients with otherwise asymptomatic low-grade pathology.[46,47]

Several other hypotheses have been proposed to explain the pathogenesis of Alzheimer's disease, including abnormalities in proteins regulating the cell cycle, inflammatory mechanisms, oxidative stress, and mitochondrial dysfunction with disruption in neuronal energy metabolism.[48–51] Although each of these mechanisms could contribute to disease pathogenesis, to what extent they drive the neurodegenerative process is uncertain.

Clinical features

Alzheimer's disease is a slowly progressive disorder, with insidious onset and progressive impairment of episodic memory; instrumental signs include aphasia, apraxia, and agnosia, together with general cognitive symptoms, such as impaired judgment, decision-making, and orientation.

The term Alzheimer's disease was originally reserved for individuals with presenile onset of symptoms, whereas the expression senile dementia was used when onset was after 65 years of age. Largely on the basis of histopathological observations that plaques and tangles are present in the brains of patients with Alzheimer's disease and those with senile dementia, these disorders have been held to represent a single, homogeneous entity. However, the instrumental signs, the plaque and tangle load, and the cholinergic deficits are more severe in early-onset Alzheimer's disease than in senile dementia.[52,53] In fact, based on plaque and tangle load, it may be difficult to distinguish elderly patients with Alzheimer's disease from non-demented individuals of the same age.[54,55] Furthermore, in young patients with Alzheimer's disease there is a strong correlation between dementia severity and plaque and tangle burden, whereas this association is not found in elderly patients with the disease.[56] These data question the scientific basis for combining early-onset Alzheimer's disease and senile dementia. Thus, whether these disorders constitute one homogeneous entity, are separate diseases, or represent a continuum of an intensified ageing process is uncertain.[57,58]

Neurodegeneration in Alzheimer's disease is estimated to start 20–30 years before clinical onset.[59] During this preclinical phase, plaque and tangle load increase and at a certain threshold the first symptoms appear. This clinical phase is often designated mild cognitive impairment (MCI), which is defined on the basis of subjective reports of memory loss that are verified by close personal informants and by objective measures adjusted for age and education.[60] MCI is an aetiologically heterogeneous entity because many patients with MCI have prodromal Alzheimer's disease, whereas others have a benign form of MCI as part of the normal ageing process and some have other disorders such as vascular dementia.[61] The memory-predominant subtype amnestic MCI has been suggested to constitute a transitional stage between normal ageing and Alzheimer's disease,[60] but data show that many patients with amnestic MCI have the early neuropathological changes of Alzheimer's disease, and thus, in reality, represent early Alzheimer's disease.[62] In MCI, the conversion rate to Alzheimer's disease with clinical dementia is 10–15% per year.[60,63]

Diagnosis

The medical history together with the clinical, neurological, and psychiatric examination serves as the basis in the diagnostic work-up. In very early cases, neuropsychological testing can help to obtain objective signs of memory disturbances. Laboratory studies, such as thyroid-function tests and serum vitamin B12, are necessary to identify secondary causes of dementia and coexisting disorders that are common in elderly people.

Neuroimaging, CT and MRI, plays an important part in the diagnosis of Alzheimer's disease to exclude alternative causes of dementia, such as brain tumour and subdural haematoma. Cerebral atrophy, visualised as enlarged ventricles and cortical sulci, is also identified by CT and MRI, but the overlap with normal ageing and other dementias is too large to have any diagnostic value.[64] However, neuroimaging is valuable to detect cerebrovascular disease, such as cerebral infarcts and white-matter lesions, which is of importance to identify vascular dementia or mixed dementia (Alzheimer's disease/vascular dementia).

The criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), which are commonly used for the clinical diagnosis of Alzheimer's disease, were published more than 20 years ago.[65] These criteria for probable Alzheimer's disease largely depend on the exclusion of other dementias. Even in patients who have been followed up clinically for several years at expert research centres, the diagnostic accuracy is relatively low, with sensitivity of around 80% and specificity of 70%,[66] figures that are probably substantially lower in primary care settings and in patients with mild Alzheimer's disease. Another weakness with these criteria is that they do not specify how to deal with concomitant cerebrovascular disease. This results in inconsistencies in what degree of infarcts, lacunas, or white-matter changes are allowed before a diagnosis of mixed dementia is made.

A definite diagnosis of Alzheimer's disease can only be made by neuropathology,[65] which is regarded as the gold standard. Large community-based neuropathology studies show that a substantial proportion (20–40%) of non-demented individuals have enough plaques and tangles to warrant a neuropathological diagnosis of Alzheimer's disease.[47,67] Additionally, around 50% of patients with neuropathological disease have significant concomitant cerebrovascular pathology,[47,67,68] and there is also a large overlap in pathology between Alzheimer's disease and Lewy-body dementia (LBD).[69] Altogether, as

few as a third of patients with definite Alzheimer's disease have pure Alzheimer pathology.[68] These data show that the gold standard is not pure gold.

Furthermore, according to the NINCDS-ADRDA criteria, Alzheimer's disease cannot be diagnosed until the patient has Alzheimer's dementia, meaning cognitive signs severe enough to exceed an arbitrary threshold of interference with social or occupational activities. The promise of new disease-modifying drugs that are likely to be most effective in the earlier stages of the disease, before neurodegeneration is too severe, together with the finding that amnestic MCI often represents Alzheimer's disease at its earliest symptomatic stage,[62] have created a need for criteria revision.[70]

New biomarkers would be of great value as diagnostic tools, both for the clinical diagnosis of Alzheimer's disease and the prediction of incipient Alzheimer's disease in MCI cases. Criteria for an ideal biomarker of the disease have been proposed by the Consensus Group on Molecular and Biochemical Markers of Alzheimer's disease.[71] In short, an ideal biomarker for the disease should detect a fundamental characteristic of the neuropathology and be validated in neuropathologically confirmed cases, with sensitivity and specificity of no less than 80%.[71]

Some methods show promise as diagnostic tools for the disease, including MRI measurements of medial temporal lobe atrophy, positron emission tomography (PET) imaging of glucose metabolism and Aβ deposits, and CSF biomarkers. At present, none of these are recommended in any consensus guidelines for diagnosis of the disease, but if validated in large prospective studies, these biomarkers could be incorporated in future refined diagnostic criteria.

MRI medial temporal lobe atrophy

The first degenerative changes in the disease occur in the medial temporal lobe, including the hippocampus and entorhinal cortex.[39] Indeed, hippocampal atrophy is present in the disease as shown in both CT and MRI studies.[72,73] A substantial number of studies have shown that MRI measurements of hippocampal atrophy can distinguish Alzheimer's disease from cognitively normal elderly people with 80–90% accuracy.[74] However, only a few MRI studies have addressed the differentiation of Alzheimer's disease from other dementias, and there are few autopsy confirmation data available. Most studies have shown that hippocampal and entorhinal cortex atrophy is also present in other dementias, such as frontotemporal dementia and vascular dementia.[75,76] Thus, available results do not point to clear strategies for differentiation based on MRI, and thus MRI medial temporal lobe measurement was not recommended for routine use by the American Academy of Neurology.[66]

Hippocampal atrophy can predict the progression from MCI to Alzheimer's disease (figure 5), but the overlap is too large to have a prognostic value in individual patients.[77] Additionally, since both ageing and Alzheimer's disease are independently associated with reduced hippocampal volume, age-dependent criteria for hippocampal atrophy are needed.[78] Entorhinal cortex volume might precede hippocampal atrophy in Alzheimer's disease and has a high predictive value for incipient disease in MCI.[79,80]

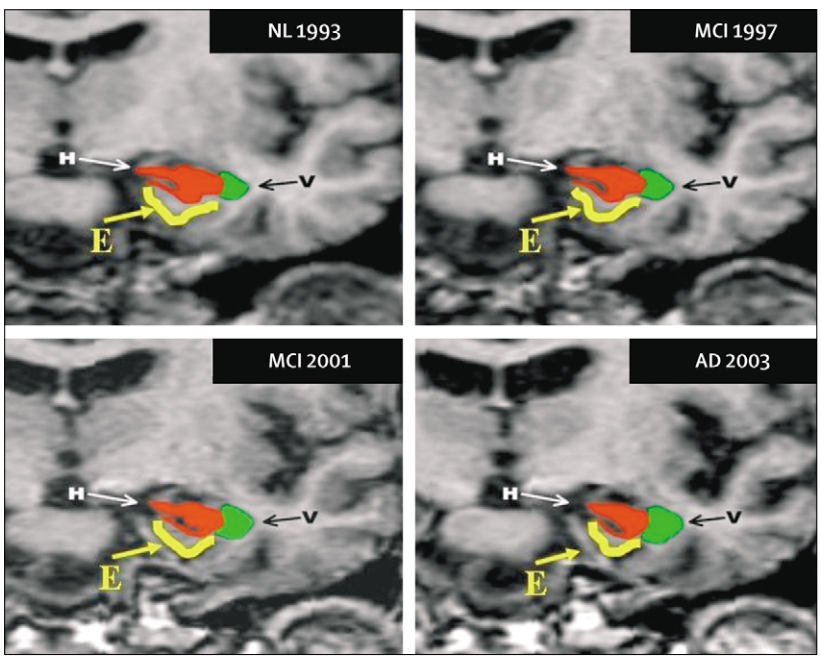

Figure 5: **Longitudinal structural changes on MRI**
MRI scans in a 75-year-old cognitively normal man at baseline (1993) and over 10 years. During this observation period the patient declined to MCI and was later diagnosed with Alzheimer's disease. High-resolution coronal T1-weighted image sets were co-registered, and three regions from each observation are shown: the hippocampus (red), the entorhinal cortex (yellow), and the CSF containing ventricle (green). The images show that the hippocampus and entorhinal cortex typically get smaller, whereas the ventricle increases in size with disease progression.

Positron emission tomography

Hypometabolism in the temporal, parietal, and posterior cingulate cortex, identified by ^{18}F-fluorodeoxyglucose (FDG) PET, could be used to differentiate with high sensitivity patients with Alzheimer's disease from cognitively normal elderly people.[74] For example, a large multicentre study showed 93% sensitivity and specificity for distinction of Alzheimer's disease from normal indiviuals.[81] Also, FDG-PET has a relatively high ability to differentiate Alzheimer's disease from other dementias, especially from frontotemporal dementia, which has been confirmed in studies with autopsy.[82,83]

Temporoparietal hypometabolism on FDG-PET might also predict the progression from MCI to Alzheimer's disease with high accuracy.[84,85] Additionally, PET coupled with MRI co-registration to guide anatomical sampling enables detection of hippocampal glucose metabolism. Hippocampal region FDG-PET changes are associated with the clinical decline from normal to MCI or Alzheimer's disease (figure 6).[86] Regional metabolic

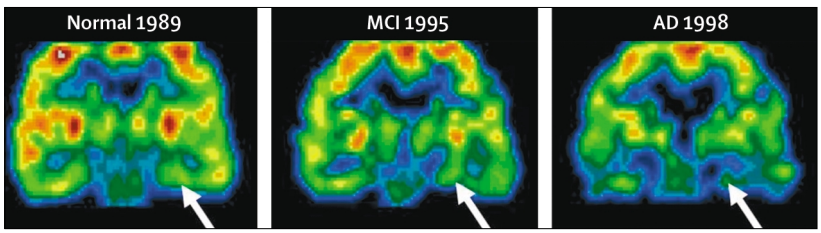

Figure 6: **Longitudinal metabolic reductions on FDG-PET**
FDG-PET scans in a 71-year-old cognitively normal woman at baseline (1989) and over 9 years. During this observation period the patient declined to MCI and later was diagnosed with Alzheimer's disease, which was confirmed at autopsy. For each observation a coronal PET scan is depicted at the level of the entorhinal cortex and anterior hippocampus. Arrows point to the inferior surface of the entorhinal cortex with progressively darker colours on the PET scans, which indicates progressive reductions in glucose metabolism.

changes on FDG-PET might also predict the decline from MCI to Alzheimer's disease better than volumetric MRI.[87]

In a PET study, use of the thioflavin T derivative Pittsburgh Compound-B (PIB) was shown to enable imaging of fibrillar Aβ plaques in the living human brain.[88] Patients with Alzheimer's disease typically show marked PIB retention in cortical areas known to contain large amounts of Aβ plaques (figure 7). At the time of this writing, amyloid imaging studies have not yet reported on early diagnosis, longitudinal change, or differential diagnosis. Other Aβ plaque imaging techniques using PET and MRI are also in development.[89]

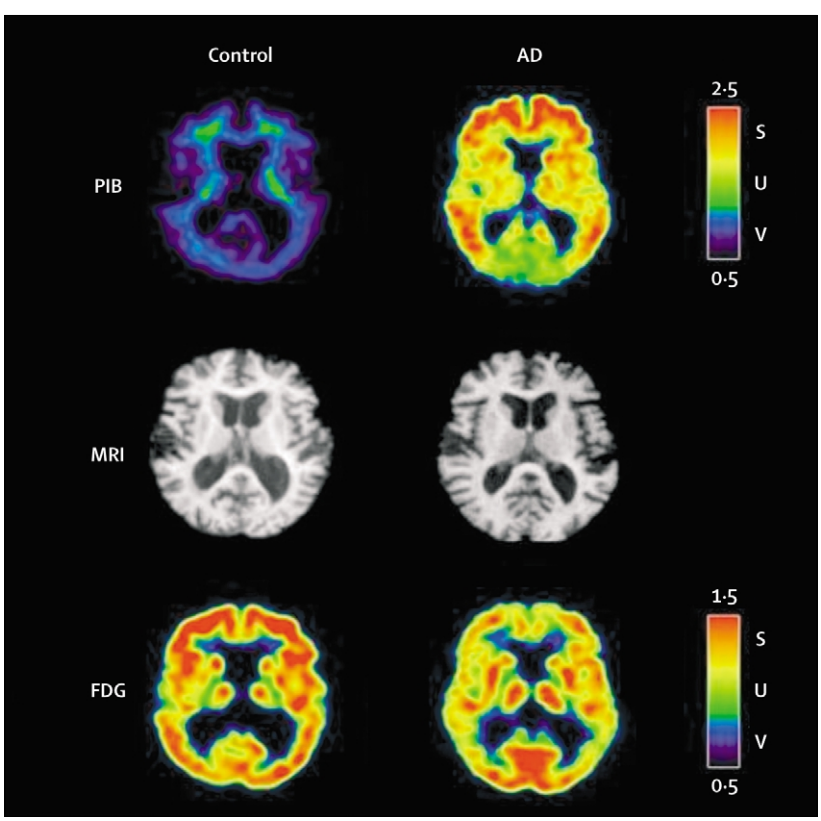

Figure 7: **Comparison of PIB images, MRI, and FDG-PET images from a cognitively normal person and a patient with mild Alzheimer's disease**
The normal individual was 71 years of age and had an MMSE score of 30, whereas the patient with Alzheimer's disease was 69 years of age and had an MMSE of 21. The Alzheimer's disease patient has marked PIB accumulation together with an FDG scan typical for the disease with temporoparietal and frontal hypometabolism. Scale bars indicate standardised uptake values (SUV) for PIB and FDG. Note that the dynamic range of PIB is twice that of FDG. Courtesy of University of Pittsburgh Amyloid Imaging Group.

CSF biomarkers

The diagnostic accuracy of the CSF biomarkers total tau (T-tau), phosphorylated tau (P-tau), and Aβ42 has been assessed in several studies.[90] CSF T-tau is increased to around 300% of control concentration in Alzheimer's disease, probably as a result of neuronal and axonal degeneration. In ten large prospective studies on consecutive patients, mean sensitivity was 84% while the specificity against cognitively normal elderly people was 91%.[91] By contrast, CSF-Aβ42 is reduced to around 50% of control concentrations, which may be associated with the deposition of the peptide in plaques with lower concentrations diffusing to the CSF. Six large prospective studies on consecutive patients show a mean sensitivity for Alzheimer's disease of 89%, with a specificity of 90% against cognitively normal elderly people.[91] The diagnostic accuracy of these biomarkers has also been validated in neuropathologically confirmed cases.[92]

Normal CSF T-tau and Aβ42 concentrations are found in several important differential diagnoses, such as depression and Parkinson's disease, but the ability to differentiate Alzheimer's disease from other dementias, such as frontotemporal dementia and Lewy-body dementia, is not ideal.[90] However, several reports have shown that the addition of CSF P-tau increases the ability to differentiate Alzheimer's disease from other dementias, reaching specificity figures of above 80%.[93]

Recent research on CSF biomarkers has focused on early diagnosis, and several studies have shown a high predictive value for identification of prodromal Alzheimer's disease in MCI.[94] A large study with extensive clinical follow-up that assessed the ability of CSF biomarkers to predict incipient Alzheimer's disease in MCI cases reported a sensitivity of 95% at a specificity of 83–87% for different combinations of biomarkers.[95]

Treatment

Knowledge of the neurotransmitter disturbances in Alzheimer's disease has led to the development of drugs with symptomatic effects, which are approved in many countries. Research advances in the molecular pathogenesis of Alzheimer's disease have also led to new drug candidates with disease-modifying potential, which have now come to testing in clinical trials. Epidemiological data have suggested additional drug candidates, some of which have been investigated in randomised trials.

Symptomatic treatments

Acetylcholinesterase inhibitors

The cholinergic hypothesis in Alzheimer's disease states that degeneration of cholinergic neurons in the

basal forebrain nuclei causes disturbances in presynaptic cholinergic terminals in the hippocampus and neocortex, which is important for memory disturbances and other cognitive symptoms.[96]

One therapeutic approach to enhance cholinergic neurotransmission is to increase the availability of acetylcholine by inhibiting acetylcholinesterase, the enzyme that degrades acetylcholine in the synaptic cleft. The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine are approved for clinical use in Alzheimer's disease (table 1). Donepezil and galantamine are selective acetylcholinesterase inhibitors, whereas rivastigmine inhibits acetylcholinesterase and buturylcholinesterase with similar affinity and galantamine also allosterically modulates presynaptic nicotinic receptors. Both donepezil and galantamine are metabolised in the liver by the cytochrome P450 enzymes CYP2D6 and CYP3A4, and can thus interact with drugs that inhibit these enzymes, such as fluoxetine and paroxetine, with resulting cholinergic adverse events. Rivastigmine has a non-hepatic metabolism, making interactions rare. The half-life of the drugs also varies, which determines the need for one or two doses per day. Other differences are whether the drug has to be coadministered with food. The clinical relevance of these differences in pharmacology and pharmacokinetics is unknown.

The efficacy of these drugs has been studied in more than 30 randomised double-blind clinical trials. Most trials have been for 3–6 months and have shown modest positive effects on cognitive symptoms, with a mean treatment effect of 2·7 points on the Alzheimer's disease assessment scale, cognitive subscale (ADAS-Cog) and 1·4 points on the mini-mental state exam (MMSE).[97] Benefits of acetylcholinesterase inhibitors are also seen for functional and behavioural symptoms. There is no evidence that these drugs differ in efficacy.[97]

Considering the mechanism of action for the acetylcholinesterase inhibitors, they are not expected to change the natural course of Alzheimer's disease, but only to temporarily mitigate some of the symptoms. However, some studies have shown that they can be effective for up to 2 years,[98,99] and open-label extension studies suggest that some patients can have long-term benefits for up to 5 years.[100]

One trial showed positive effects of donepezil on cognition and activities of daily living for 6 months in patients with severe Alzheimer's disease.[101] Furthermore, in MCI a reduced probability of progression to Alzheimer's disease was shown after a year, which did not persist after 3 years of treatment.[102] However, clinical MCI trials are hampered by the fact that current MCI criteria only have a low to moderate accuracy for identification of incipient Alzheimer's disease.[63] In other words, a significant proportion of the included cases do not have the disorder for which the treatment is intended, which will limit the possibility of identifying a drug effect on the conversion rate to Alzheimer's disease.

A Cochrane Review concluded that the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine are efficacious in mild to moderate Alzheimer's disease,[97] and these drugs are also recommended by the Quality Standards Subcommittee of the American Academy of Neurology as first-line pharmacotherapy for symptomatic treatment of the disease.[103]

Overall, they are safe drugs, and side-effects are generally limited to gastrointestinal symptoms, including nausea, vomiting, and diarrhoea. The occurrence of side-effects can usually be reduced by starting treatment with a low dose, which is escalated slowly (table 1). Coadministration with food delays absorption of the drug and can also reduce gastrointestinal side-effects.

Treatment guidelines, such as those of the National Institute for Health and Clinical Excellence (NICE) in the UK, recommend that acetylcholinesterase inhibitor treatment should be continued only if there is an increase, or no decrease, in MMSE score 2–4 months after reaching the suitable dose. However, definition of the lack of drug benefit is a difficult task in view of the variable clinical

For **NICE guidelines** see http://www.nice.org.uk

	Donepezil	Galantamine	Rivastigmine	Memantine
Indication	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Moderate to severe AD
Mode of action	Selective AChE inhibition	Selective AChE inhibition and allosteric nicotine receptor modulation	Slowly reversible AChE and BuChE inhibition	Non-competitive NMDA-receptor antagonist
CYP450 metabolism	Yes (CYP2D6 and CYP3A4)	Yes (CYP2D6 and CYP3A4)	No, hydrolysed by esterases	No
Half-life	Long (70 h)	Short (7–8 h)	Very short (1 h)	Long (60–100 h)
Doses per day	One	Two (tablets) One (prolonged release capsule)	Two	Two (first week once a day)
Given with food	Irrelevant	Recommended	Yes (increased bio-availability)	Irrelevant
Initial dose	5 mg/day	8 mg/day	3 mg/day (1·5 mg×2)	5 mg/day
Dose escalation	4–6 weeks	Every 4 weeks, up to recommended or tolerated dose	Every 2 weeks, up to recommended or tolerated dose	Every week, up to recommended or tolerated dose
Recommended clinically efficient dose	10 mg/day	16–24 mg/day	6–12 mg/day	20 mg/day

AD=Alzheimer's disease. AChE=acetylcholinesterase. BuChE=buturylcholinesterase. CYP450=cytochrome P450. NMDA=N-methyl-D-aspartate.

Table 1: **Characteristics of drugs for symptomatic treatment of Alzheimer's disease**

course between patients and given that the within-patient variation in MMSE score in placebo-treated patients can be up to 5 points over a month. Thus, discontinuation of drug treatment because of lack of response must be a decision in which both the variable clinical course and ethical issues are considered.

Several other therapeutic approaches to enhance cholinergic neurotransmission, such as precursor loading with choline and lecithin, muscarinic (M1) receptor agonists, and nicotine and other nicotinic agonists, can improve memory and attention in young individuals, but have no proven clinical usefulness in Alzheimer's disease.[104]

Memantine

Glutamate is the major excitatory neurotransmitter in the brain. Under normal conditions, glutamate and the *N*-methyl-D-aspartate (NMDA) receptor have important roles for learning and memory processes. Under abnormal conditions, such as in Alzheimer's disease, increased glutamatergic activity can lead to sustained low-level activation of NMDA receptors, which may impair neuronal function.[105]

Memantine is a non-competitive NMDA-receptor antagonist that is believed to protect neurons from glutamate-mediated excitotoxicity without preventing the physiological NMDA-receptor activation needed for cognitive functioning.[106] Randomised double-blind clinical trials show modest positive effects on cognitive and behavioural symptoms, and improved ability to perform activities of daily living at 6 months in people with moderate to severe Alzheimer's disease.[106] Additionally, in moderate to severe disease, combination therapy with donepezil and memantine show positive effects on symptoms relative to donepezil alone.[107] However, a Cochrane Review concluded that there are no data to lend support to the notion that memantine has any beneficial effect in mild disease.[105]

Despite the theoretical rationale for neuroprotective properties of memantine, current trials are too short to assess if the drug has any disease-modifying effects. Nevertheless, the drug is well tolerated in general, with few adverse events, and may be a useful therapeutic adjunct in patients with moderate to severe disease, typically defined as an MMSE less than 15 points.[105]

Treatment of behavioural signs

Behavioural signs, such as aggression, psychomotor agitation, and psychosis (hallucinations and delusions), are very common in patients with Alzheimer's disease, especially in the late stages of the disease. Such symptoms not only affect quality of life for patients and caregivers, but also contribute to care burden and economic cost.

Atypical antipsychotic drugs produce fewer extrapyramidal side-effects (eg, parkinsonism and tardive dyskinesia) than do conventional neuroleptics, and are thus preferred for the management of psychosis or agitation. Several short-term trials show efficacy of risperidone and olanzapine in reducing the rate of aggression, agitation, and psychosis.[108,109] Alternative treatments include anticonvulsants, such as divalproate and carbamazepine, and short-acting benzodiazepines, such as lorazepam and oxazepam.[110] Additionally, the cholinergic deficits can contribute to the development of behavioural symptoms, and treatment with acetylcholinesterase inhibitors also shows improvements in behavioural symptoms.[96]

Drug candidates with potential disease-modifying effects

Substantial efforts have been made to translate the advances in the molecular pathogenesis of Alzheimer's disease into therapeutic strategies. The major focus has been to inhibit brain Aβ production and aggregation, and to increase Aβ clearance from the brain.

Secretase modulators

The finding that BACE1 knockout mice have abolished Aβ production without any clinical phenotype[111] made BACE1 inhibitors an attractive therapeutic strategy. β-secretase inhibitors have been developed to reduce brain Aβ concentrations in Alzheimer's disease transgenic mice.[112] For γ-secretase there is a concern about adverse effects because it cleaves other substrates such as Notch.[25] Nevertheless, γ-secretase inhibitors have been developed that do not affect Notch signalling,[113] and have shown good tolerability in phase I studies.[114] Drugs that stimulate α-secretase can shift APP processing towards the non-amyloidogenic pathway, thus reducing Aβ production. Bryostatin, a protein kinase C activator currently tested in clinical trials as an anticancer drug, substantially enhances α-secretase processing of APP and reduces brain Aβ42 concentrations in Alzheimer's disease transgenic mice.[115]

Aβ immunotherapy

The principle of Aβ immunotherapy was first reported in a paper showing that active immunisation of Alzheimer's disease transgenic mice with fibrillar Aβ attenuated Aβ deposition.[116] Similar results were obtained by use of passive immunisation with antibodies against Aβ.[117] The effect might be mediated by anti-Aβ antibodies that bind to Aβ plaques and induce Aβ clearance by microglia,[117,118] or alternatively bind soluble Aβ in the periphery, thereby driving an Aβ efflux from the brain. These results were the basis for initiating clinical trials with active immunisation with the vaccine AN1792, composed of preaggregated Aβ42.[118] However, the phase IIa AN1792 trial had to be interrupted because 6% of cases developed encephalitis.[119] This side-effect has been suggested to be due to a T-cell response against the mid-terminal and C-terminal part of the peptide.[118] The second generation of immunotherapy, Aβ immunoconjugates composed of the N-terminal part of Aβ conjugated to a carrier protein,[118] or virus-like particles, could allow for active immunisation with reduced

risk of Th-1 mediated side-effects. Both active immunisation with N-terminal Aβ fragments and passive immunisation with humanised anti-Aβ monoclonal antibodies are now in phase II trials.

Aβ fibrillisation inhibitors

Small peptides that interfere with Aβ-Aβ or Aβ-ApoE interactions can prevent the conformational change of Aβ to β-sheet structure and subsequent fibrillisation. Two such peptides have been shown to reduce Aβ fibrillisation in vitro and brain Aβ load in Alzheimer's disease transgenic mice, without inducing an immune response.[120,121] Glycosaminoglycans bind Aβ and can promote its aggregation.[122] The drug candidate NC-531 (Alzhemed) is a glycosaminoglycan mimetic designed to interfere with the association between glycosaminoglycans and Aβ,[123] but the paucity of publications precludes a more detailed review. A phase III clinical trial is ongoing. Copper and zinc ions can induce Aβ aggregation and toxic effects. The metal chelator clioquinol (PBT-1) reduces brain Aβ deposition in Alzheimer's disease transgenic mice.[124] A small phase II trial showed marginal cognitive improvements with clioquinol,[125] but because of toxic impurities (a di-iodo form of clioquinol) during production, further clinical trials have been halted. A new drug, PBT-2, which does not contain iodine, is currently undergoing clinical trials.

Anti-tau drugs

Drug candidates that reduce tau phosphorylation by inhibiting tau kinases, such as CDK5 and GSK-3β, are in the preclinical phase. However, since tau phosphorylation is regulated by the balance between multiple kinases and phosphates,[38] inhibition of a single kinase might be insufficient to normalise tau phosphorylation.

Drug candidates based on epidemiology

Epidemiological studies have served as the theoretical basis for several treatment approaches. As reviewed below, observational studies have suggested a protective effect of different types of drugs or supplements, but when tested in randomised controlled clinical trials designed to avoid the many potential biases and inherent methodological problems in epidemiological studies, beneficial effects have been difficult to ascertain.

Anti-inflammatory drugs

Plaques in Alzheimer's disease are accompanied by local inflammatory characteristics, but whether the inflammation contributes to neurotoxic effects or represents a secondary reaction to Aβ deposition is unclear.[49] Most epidemiological studies suggest that the risk of the disease is reduced in patients treated with non-steroidal anti-inflammatory drugs (NSAIDs).[49] Several, but not all, NSAIDs reduce brain Aβ burden in Alzheimer's disease transgenic mice, which may be mediated by either inhibition of cyclo-oxygenase (COX), or by a direct effect on γ-secretase, thereby reducing Aβ generation independently of COX inhibition.[126]

Clinical trials on anti-inflammatory drugs, including prednisone, hydroxychloroquine, and the selective COX-2 inhibitors celecoxib and rofecoxib, showed no effects on cognition in Alzheimer's disease.[49] The first large-scale clinical trial on both non-selective and COX-2 selective NSAIDs in the disease was also disappointing.[127] One explanation is that these drugs might be protective only if given during mid-life, but will not reverse the degenerative process in patients with established pathology. A primary prevention trial of NSAIDs has been started to test whether they can be protective in patients with MCI.[49]

Cholesterol-lowering drugs

The first link between cholesterol and Alzheimer's disease was suggested in a study reporting that rabbits fed with very high-cholesterol diet develop intracellular Aβ accumulation.[128] However, when feeding Alzheimer's disease transgenic mice a high-cholesterol diet, both reduced[129] and increased[130] brain Aβ load has been reported. Retrospective case-control studies suggesting that treatment with cholesterol-lowering drugs (statins) reduce the incidence of the disease have received much attention.[131,132] Subsequent studies on Alzheimer's disease transgenic mice also suggested that cholesterol-lowering drugs diminish brain Aβ load.[133] However, more recent prospective cohort studies have not shown any association between statin use and reduced risk of the disease.[134,135] Furthermore, treatment trials in patients with the disease have not reported any change in plasma or CSF Aβ42,[136,137] and a 12-month placebo-controlled double-blind study on atorvastatin showed only borderline cognitive improvement.[138] Large randomised clinical trials with long treatment periods are ongoing.

Oestrogens

Epidemiological studies have reported an association between reduced risk of dementia and postmenopausal oestrogen supplementation.[139,140] Animal studies also suggest that oestrogens could have several beneficial effects on neuronal function.[141] However, large randomised controlled clinical trials of oestrogens have not shown a reduced risk of the disease.[142,143]

Antioxidants

Large observational studies suggest that dietary intake of antioxidants, such as vitamin E, could reduce the risk of the disease.[144,145] One randomised controlled clinical trial of vitamin E supplementation in the disease showed only a marginal effect on time to institutionalisation and need of care.[146] However, another well-designed randomised controlled trial showed no effect of vitamin E supplementation on the rate of progression to Alzheimer's disease in MCI.[102]

	Treatment	Mechanism of action	Mouse model	Reference
Secretase modulation	[OM00-3]DR9	β-secretase inhibitor	Tg2576	112
	DAPT	γ-secretase inhibitor	PDAPP	152
	Bryostatin	PKC activator, α-secretase stimulator	$APP_{V717I}/PS1_{A246E}$	115
Aβ immunotherapy	Pre-aggregated Aβ1-42+adjuvant	Active immunisation	PDAPP	116
	Anti-Aβ antibodies	Passive immunisation	PDAPP	117
Anti-aggregation	iAβ5p peptide	β-sheet breaker peptide	$APP_{V717I}/PS1_{A246E}$	120
	Aβ12-28P peptide	ApoE-Aβ binding blocker	$APP_{Swe}/PS1_{M146L}$	121
	Neprilysin gene transfer	Increased Aβ degradation	PDAPP	153
Lipid/carbohydrate metabolism modulation	BM15.766	Cholesterol lowering	Tg2576	133
	High cholesterol diet	Cholesterol challenge	APP_{Swe}	129
	Caloric restriction	Reduced insulin levels	$APP_{Swe/Ind}$	154
	High saturated fat/low carbohydrate diet	Unkown. Ketogenic diet?	APP_{V717I}	155
	CP-113,818	ACAT inhibitor	APP_{Swe} and APP_{V717I}	156
	Omega-3 fatty acid	Altered APP processing? Anti-oxidative?	Tg2576	157
	T0901317	Liver X receptor ligand	APP23	158
Kinase modulation	Wortmannin	Phosphatidyl-inositol kinase inhibitor	Tg2576	159
	Lithium	GSK3β inhibition	PDAPP	160
	Valproic acid	GSK3β inhibition	PDAPP	160
Anti-inflammatory/anti-oxidative	NSAIDs (8 FDA-approved drugs)	Anti-inflammatory	Tg2576	126
	NCX-2216	Anti-inflammatory, anti-oxidative, NO-release	$APP_{Swe}/PS1_{M146L}$	161
	Pioglitazone	PPARγ-agonist, anti-inflammatory	APP_{V717I}	162
	Lipopolysaccharide	Activation of the innate immune system	Tg2576	163
	Curcumin (curry spice)	Anti-inflammatory, anti-oxidative	Tg2576	164
	Vitamin E	Anti-oxidative	Tg2576	165
	N-acetyl cysteine	Anti-oxidative	TgCRND8	166
Neurotransmitter modulation	Nicotine	Cholinergic stimulation	Tg2576	167
	AF267B	Selective M1 muscarinic agonist	3×Tg AD mice	168
	PEC	Butyrylcholinesterase inhibitor	$APP_{Swe}/PS1_{A246E}$	169
	Paroxetine	Serotonin re-uptake inhibitor	TgCRND8	166
Hormone modulation	17α-oestradiol and 17β-oestradiol	Hormone replacement	Tg2576	170
	Leuprorelin	Gonadotropin-releasing hormone agonist	Tg2576	171
	Melatonin	Unknown. Multiple potential mechanisms	Tg2576	172
Environmental exposure	Environmental enrichment	Unknown	$APP_{Swe}/PS1_{\Delta E9}$	173
	Experimental acute brain trauma	Unknown. Aβ clearance by microglia?	PDAPP	174
Heavy metal modulation	Dietary copper	Copper supplementation	APP23	175
	Clioquinol	Copper/zinc chelator	Tg2576	124
	DP-109	Heavy metal chelator	Tg2576	176
Miscellaneous	Cerebrolysin (porcine brain peptide mix)	Neurotrophic	mThy1-hAPP751	177
	Enoxaparin (low MW heparin)	Unknown.	APP23	178
	RAGE	Blockage of Aβ transport to the brain?	APP_{Swe}/APP_{V717F}	179
	Insulin-like growth factor I (IGF-I)	Increased Aβ elimination from brain?	APP/PS2	180
	Epigallocatechin-3-gallate (green tea)	Unknown. α-secretase stimulation?	Tg2576	181
	Erythromycin	Macrolide antibiotic	TgCRND8	166
	Soluble Nogo-66 receptor fragment	Unknown. Multiple potential mechanisms.	$APP_{Swe}/PS1_{\Delta E9}$	182
	Rosiglitazone	Increased insulin sensitivity? Cortisol lowering?	Tg2576	183
	Propentofylline	Unknown. Multiple potential mechanisms	Tg2576	184

Experiments based on transgenic co-expression of another protein are not included. For details on the transgenic mouse models, see reference 151.

Table 2: **Treatment strategies to lower Aβ concentrations and plaque load in Alzheimer's disease transgenic mouse models**

Future prospects

The past two decades of Alzheimer's disease research have resulted in detailed knowledge of the molecular mechanism of Aβ production and aggregation. With the amyloid cascade hypothesis serving as the foundation, and the Alzheimer's disease transgenic mouse models as the tools for testing, anti-Aβ drug candidates have been developed. Several phase II clinical trials are now

ongoing or under planning. The key question that will determine whether these will be successful is not only whether the amyloid cascade hypothesis is correct—ie, whether Aβ deposition is the cause or consequence of neurodegeneration in sporadic Alzheimer's disease—but also whether the transgenic mouse models are accurate models for sporadic Alzheimer's disease.

Because of similarities in clinical presentation and pathology, the amyloid cascade hypothesis is also thought to apply to sporadic disease. Besides the association between APOE and Aβ deposition,[20] the evidence for the hypothesis emanates from studies on familial Alzheimer's disease and from animal and cellular models based on the mutations associated with familial disease. This notion introduces the risk that the hypothesis might not be valid for sporadic disease where clarification of the molecular pathogenesis has been more elusive.

Data show that axonal defects can precede Aβ deposition and further promote the amyloidogenic process both in transgenic mouse models and in patients with the disease.[147] Other data also lend support to axonal dysfunction as an early event in Aβ deposition.[18] Both human and experimental studies on brain trauma, where axonal damage is the main lesion, have shown that there is an accumulation of APP, BACE1, and presenilin in the damaged axons, followed by an increase in Aβ with plaque development.[148,149] Similarly, cerebral ischaemia results in upregulation of APP expression with Aβ generation followed by Aβ deposition.[44,45] Furthermore, in the gracile axonal dystrophy mouse, which develops axonal degeneration due to a mutation in the ubiquitin carboxy-terminal hydrolase gene, APP increases in degenerating axons at 4 weeks of age, followed by Aβ accumulation at 9 weeks of age.[150] These data show that Aβ accumulation and deposition can occur secondary to axonal damage and degeneration, which could even represent the brain's attempt to launch repair mechanisms.

Genetically engineered mice that harbour mutated human *APP* or *presenilin* genes develop progressive diffuse and fibrillar Aβ pathology with age[151] and are commonly used to assess treatment strategies. A reduction in Aβ plaques and brain Aβ concentrations, often called Aβ load or Aβ burden, is the desired treatment response. We have counted 46 different treatment strategies that resulted in an often substantial (50–90%) reduction in Aβ load in Alzheimer's disease transgenic mice (table 2).[112,115–117,120,121,124,126,129,133,152–184] We do not consider it likely that all, or even most, of these treatments will also result in a significant reduction in Aβ load and improve cognitive functioning or delay progression in sporadic disease. Indeed, treatment with nicotine or vitamin E for some months results in a large (70–80%) reduction in brain Aβ burden in transgenic mouse models,[165,167] but does not improve cognition in patients with Alzheimer's disease or MCI.[102,104]

Transgenic mice do not develop tangles and show only marginal neurodegeneration, despite the huge Aβ burden.[151] They have at least an eight-fold life-long overexpression of one or more foreign mutated proteins, have a short life-span, and develop Aβ plaques within some months.[151] These mice might be more responsive to anti-Aβ treatment than people with sporadic Alzheimer's disease, thus introducing a risk of an overestimation of the benefit of new treatment strategies. This notion calls for caution when translating data from mice to man. We believe that the future lies in bringing advances in basic research, technological developments, and progress in clinical research together to reach the goal of true prevention therapy for Alzheimer's disease.

Contributors

All authors participated in the writing and editing of the manuscript.

Conflict of interest statement

KB is listed as a co-inventor on the following patents: 10/982.545; WO2004/104597; and EP1480041. KB has received a consulting fee for an advisory board meeting from Innogenetics and from AstraZeneca and has received honoraria for giving general lectures on education courses for specialist physicians. MJdL is listed in several pending patent applications by New York University and is currently receiving educational grants from Forest Laboratories and from Jansson to host public lectures at New York University. HZ declares that he has no conflict of interest.

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