Q&A

NEUROSCIENCE

Alzheimer's disease

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The neurodegenerative disorder Alzheimer's disease is becoming more prevalent in ageing populations worldwide. The identification of effective treatments will require a better understanding of the physiological mechanisms involved, and innovative approaches to drug development and evaluation.

Lots of people are forgetful. Are there any particular warning signs of Alzheimer's disease?

Most people's memory declines a little with age, so the line between normal age-related forgetfulness and the earliest signs of Alzheimer's disease (AD) can be fine — so fine that a category of 'mild cognitive impairment', or MCI, has been created, in part to avoid diagnosing AD in people with more benign memory impairments. However, many people with MCI progress to AD. Typically, AD shows itself as a gradual loss of episodic memory (for instance, forgetting that a conversation took place the day before). This is often more apparent to others than to the patient. But AD can also present as word-finding difficulties, getting lost in familiar neighbourhoods, or more complex behavioural changes, sometimes brought on suddenly by a change in environment (such as hospitalization).

How is AD diagnosed?

Diagnosing AD with 100% certainty requires a detailed post-mortem microscopic examination of the brain. But nowadays, AD can be diagnosed with more than 95% accuracy in living patients by using a combination of tools. These include taking a careful history from patients and their families, and assessing cognitive function by neuropsychological tests. Other causes of dementia must be ruled out, such as low thyroid function, vitamin deficiencies, infections, cancer and depression. It's also crucial to differentiate AD from other neurodegenerative dementias, including frontotemporal dementia, Lewy-body dementia and Creutzfeldt–Jakob disease. Brain imaging and tests of cerebrospinal fluid (CSF) can help to distinguish AD from these conditions. Patients with AD typically show shrinkage of brain regions involved in learning and memory on magnetic resonance images, as well as decreased glucose metabolism and increased uptake of radioligands that detect abnormal protein deposits (amyloid) on positron emission tomography scans. CSF abnormalities include low levels of amyloid-β (Aβ) peptides and increased levels of the protein tau.

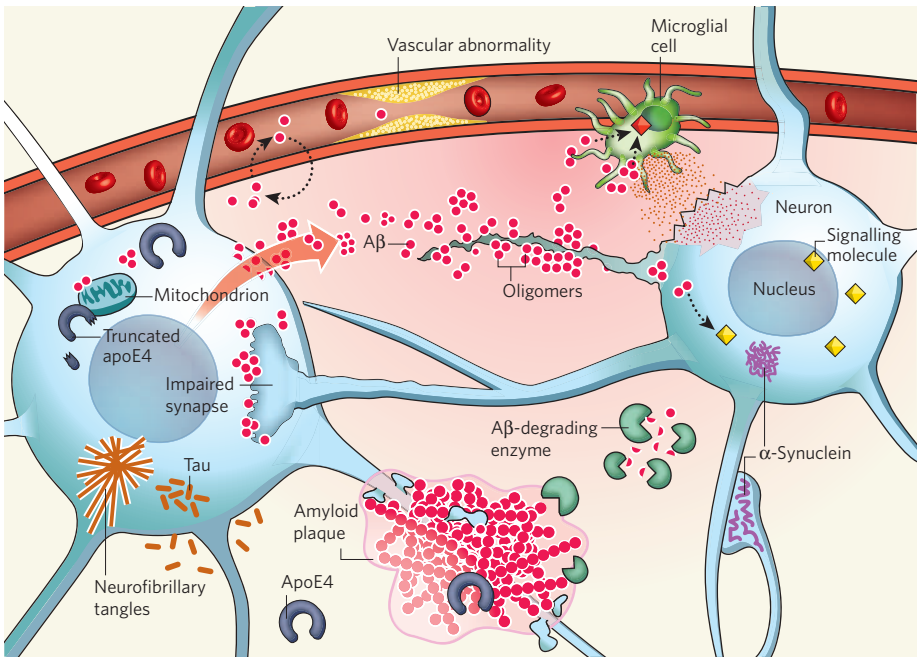

Figure 1 | Some key players in the pathogenesis of AD. Aggregation and accumulation of amyloid-β (Aβ) in the brain may result from increased neuronal production of Aβ, decreased activity of Aβ-degrading enzymes, or alterations in transport processes that shuttle Aβ across the blood–brain barrier. Aβ oligomers impair synaptic functions, whereas fibrillar amyloid plaques displace and distort neuronal processes. Aβ oligomers interact with cell-surface membranes and receptors, altering signal-transduction cascades, changing neuronal activities and triggering the release of neurotoxic mediators by microglia (resident immune cells). Vascular abnormalities impair the supply of nutrients and removal of metabolic by-products, cause microinfarcts and promote the activation of astrocytes (not shown) and microglia. The lipid-carrier protein apoE4 increases Aβ production and impairs Aβ clearance. When produced within stressed neurons, apoE4 is cleaved into neurotoxic fragments that destabilize the cytoskeleton and, like intracellular Aβ, impair mitochondrial functions. The proteins tau and α-synuclein can also self-assemble into pathogenic oligomers and can form larger intra-neuronal aggregates, displacing vital intracellular organelles. (Modified from E. D. Roberson and L. Mucke *Science* 314, 781–784; 2006.)

How big a problem is the disease?

Very big — in large part because people are living longer, and ageing is a major risk factor. The Alzheimer's Association estimates that, without better ways to prevent the disease, the number of people with AD could rise from around 5 million in the United States today to between 11 million and 16 million, and from about 26 million to more than 100 million worldwide, by 2050. This could severely strain health-care systems because the disease is so persistent, disabling and costly.

What are the causes of AD?

There are many. A lot of evidence suggests that neurodegenerative diseases, including AD, stem from the abnormal accumulation of harmful proteins in the nervous system (Fig. 1). In AD, these include Aβ peptides, the lipid-carrier protein apolipoprotein E (apoE), the microtubule-associated protein tau, and the presynaptic protein α-synuclein, which is also involved in

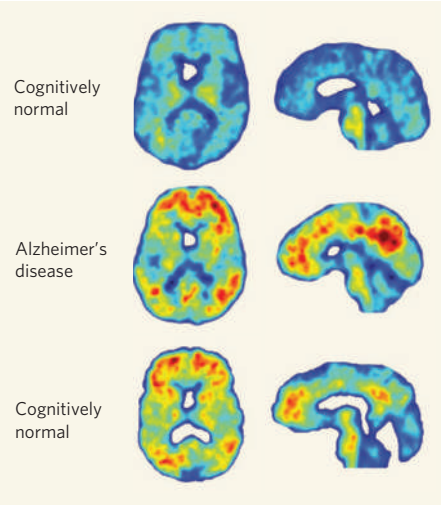

Figure 2 | The challenge of finding AD biomarkers. Two normal controls (top and bottom rows) and an age-matched AD patient (middle row) were given an intravenous injection of the radioligand PIB, which binds to fibrillar Aβ deposits. PIB retention in the brain is detected by positron emission tomography. Low levels of PIB binding (cooler colours) are seen in most cognitively normal people (top) and high levels of PIB binding (warmer colours) in people with AD (middle). But some cognitively normal people also have high levels of PIB binding (bottom), suggesting that the presence of amyloid plaques is not sufficient to cause cognitive deficits. Whether cognitively normal people with high levels of PIB binding will develop AD later on is unknown. Images courtesy of Gil Rabinovici (University of California, San Francisco) and William Jagust (Lawrence Berkeley National Laboratory).

Parkinson's disease. All of us make Aβ peptide in the brain and other organs — it's released from the amyloid precursor protein (APP) after cleavage by β-secretase and γ-secretase enzymes. But Aβ is usually quickly removed from our brains by clearance mechanisms. When its concentration is increased by overproduction or defective clearance, Aβ self-aggregates into assemblies ranging from oligomers to protofibrils, fibrils and amyloid plaques. Tau and α-synuclein can also self-aggregate into oligomers and into larger inclusions in neurons, known as neurofibrillary tangles and Lewy bodies, respectively. By definition, all patients with AD have many plaques and tangles; most patients also have Lewy bodies.

How do these changes cause cognitive decline?

This is a hotly debated issue. Most probably, Aβ and tau cause faulty neural-network activity and impair synapses between neurons that form and maintain microcircuits supporting learning, memory and other cognitive functions. Ultimately, vulnerable groups of neurons atrophy and die in a process that may involve excitotoxicity (overstimulation of neurotransmitter receptors on neuronal surface membranes), collapse of calcium homeostasis, inflammation, and depletion of energy and growth factors. A form of apolipoprotein E, apoE4, contributes to the abnormal accumulation of Aβ and tau, but probably also damages mitochondria and the cellular cytoskeleton. Aβ, tau, apoE and α-synuclein interact with many other molecules and modulate diverse signalling cascades that regulate neuronal activity and survival. Genetically modified rodents and other experimental models are being used to tease out this complexity and to determine which biochemical cascades have the greatest impact on the initiation and progression of the disease.

Can AD be inherited?

Yes. A small number of patients (probably fewer than 1%) have early-onset AD because they have inherited autosomal dominant mutations in genes whose protein products — APP, presenilin 1 (PS1) or PS2 — are involved in the production of Aβ peptides. Presenilin is the enzymatic centre of the γ-secretase complex. The most powerful genetic risk factor for the more common forms of AD is the *APOE* ε4 gene, which encodes the apoE4 lipid carrier. The more common apoE3 and the rare apoE2 forms of apoE are relatively protective against AD. More than 60% of Caucasian patients with AD carry at least one *APOE* ε4 gene. Certain variants of genes encoding another lipid carrier, clusterin (apoJ), the intracellular trafficking protein PICALM, or complement component (3b/4b) receptor 1 also modulate AD risk, possibly by affecting Aβ levels, synaptic functions or inflammation.

What about non-genetic causes?

The risk of AD may be increased by a low level of education, severe head injury, cerebrovascular disease, diabetes and obesity. But it remains uncertain whether avoiding these risk factors can significantly lower one's chances of getting the disease, especially in people with genetic risks for AD. It is likely that AD-predisposing genes interact with other disease genes and environmental factors. An otherwise healthy person may get AD early in life simply because they've inherited an aggressive *PS1* mutation. Another may get AD because they've inherited two *APOE* ε4 genes, and yet another because they've inherited one or more minor risk genes, but are also overweight and diabetic.

What has ageing got to do with it?

Ageing is the most important risk factor for AD. Even aggressive autosomal dominant AD mutations typically don't lead to obvious deficits until the fourth or fifth decade of life. Several mechanisms may protect the young brain against AD, including higher levels of growth factors, better energy metabolism and more efficient mechanisms for clearing misfolded proteins and repairing cells. Failure of these protective mechanisms may contribute to the development of AD. Ageing also increases the prevalence of obesity, diabetes and atherosclerosis, which may promote AD through metabolic or vascular mechanisms. Inflammation could be the common denominator here, as the inflammatory activity of immune cells, particularly macrophages and microglia, and of astrocytes, increases with ageing. Some of these activities are probably beneficial, whereas others may promote or allow the development of ageing-related disorders such as AD.

Are there any available treatments?

Medicines currently prescribed for AD fall into three groups: inhibitors of acetylcholinesterase; an antagonist of a receptor for the neurotransmitter glutamate; and drugs from the psychiatric toolbox to control depression and behavioural abnormalities. The neurotransmitter acetylcholine is depleted in AD brains, and inhibition of acetylcholinesterase, its degrading enzyme, aims to improve cholinergic neurotransmission. Excitotoxicity resulting from overstimulation of NMDA-type glutamate receptors may contribute to AD, providing a rationale for blocking these receptors. Several clinical trials have shown beneficial effects for inhibitors of acetylcholinesterase or NMDA receptors, although the benefits were typically small, and these drugs don't seem to arrest or reverse AD.

How about diet and lifestyle changes?

It's often suggested that adopting a healthy diet and lifestyle to avoid high cholesterol and high blood pressure may help because of the potential contribution of vascular disease to AD. Regular physical exercise also increases growth factors in memory centres of the brain. Social engagement and mental activity have also been linked to lower AD risk in epidemiological studies. In mouse models, increased activity and environmental enrichment prevent or delay the development of AD-like signs. But the control groups in many of these mouse studies were kept in rather impoverished conditions, which may have exaggerated the benefits of the 'enriched' conditions.

Are there any other treatment options?

In my opinion, one of the most productive things to do is for patients and their relatives to enrol in carefully controlled prospective clinical trials. There is an urgent need to increase the proportion of patients with AD and of healthy elderly people who participate in these trials. By contrast, dietary fads and unproven over-the-counter drugs and herbs should be discouraged. The claims to fame for these compounds are notoriously transient. They've also added a troublesome burden of confounding variables ('noise') among trial subjects and complicate the task of designing informative clinical trials.

Why have so many drug trials failed?

For several reasons. In some cases, the trial may reveal that the drug target does not have a crucial pathogenic role. In other cases, the drug may block a truly pathogenic pathway, but the overall impact may be negligible because other

branches of the multifactorial pathogenic cascade are untouched. For example, in a recent trial of an anti-Aβ agent, *APOE* ε4 gene carriers had more side effects and may have benefited less than non-carriers. Assessing whether the drug affects the most relevant target can also be challenging. Considerable evidence suggests that small Aβ oligomers cause more damage to synaptic and cognitive functions than larger amyloid plaques. Plaque loads can be estimated by radiological imaging, but brain levels of Aβ oligomers can't be reliably measured in living patients, making it unclear whether anti-Aβ treatments in clinical trials actually lower levels of the harmful Aβ oligomers. Treatment failure may also be the result of 'too little, too late'. AD probably develops insidiously over many years, if not decades. Some of my colleagues believe that even so-called early clinical stages of AD reflect advanced-stage brain failure that may be impossible to reverse.

TABLE 1 | ONGOING CLINICAL TRIALS FOR TREATING ALZHEIMER'S DISEASE

Approach or drug	Proposed mechanism of action	Phase
β-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II
γ-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II/III
Active immunization with Aβ peptides	Generates anti-Aβ antibodies that interact with Aβ and remove it from the brain by uncertain downstream mechanisms	II
Passive immunization with anti-Aβ antibodies	The antibodies interact with Aβ and remove it from the brain by uncertain downstream mechanisms	III
Intravenous pooled immunoglobulins	May enhance clearance of Aβ and other harmful proteins from the brain; may decrease harmful inflammatory processes	III
Scyllo-inositol	Decreases formation and stability of pathogenic Aβ assemblies	II
Latrepirdine	Prevents mitochondrial dysfunction	III
Inhibition of receptor for advanced glycation end products (RAGE)	Blocks stimulation of the cell-surface receptor RAGE, which binds Aβ, decreasing Aβ levels in the brain and preventing Aβ from activating pathogenic pathways	II
Stimulation of insulin signalling	Prevents hyperglycaemia; may overcome insulin resistance in the brain	II
Selective oestrogen-receptor modulator	Promotes neuroprotective effects of oestrogen without eliciting its harmful effects	II
Neurotrophic and neuroprotective agents	Stimulate neurotrophic and antioxidant pathways or pathways that protect against excitotoxicity	II

The above selection focuses on potentially disease-modifying strategies and is based on a review of websites, oral reports at scientific meetings, and discussions with Paul Aisen (University of California, San Diego) and Laurie Ryan (National Institute on Aging).

Phase II and phase III trials assess the safety and efficacy of new treatments; phase III trials involve many more subjects, are conducted in multiple centres, and are required for drug approval by regulatory agencies.

Is there any chance of disease reversal?

This depends, in part, on the 'plasticity' of the brain, which is much greater than that of other organs, although AD-associated factors such as Aβ and apoE4 may impair these adaptive mechanisms, adding insult to injury. The flip side of this coin is that removing these factors might unleash powerful repair mechanisms that could fix or help circumvent broken neural circuits so that functional recovery may be possible. Many people have shown an impressive recovery of neurological functions after extensive loss of nerve cells from other causes. The test will be to see if the AD-damaged brain is capable of similar feats when all inhibitors of effective regeneration have been eliminated.

Is stem-cell therapy an option?

The idea behind using stem cells is that these cells might be used to replace destroyed neurons. But AD poses particular challenges in this regard, as it affects diverse types of neuron in different brain regions. For now, it's unclear if stem cells can be induced to differentiate into all these cell types and if the resulting neurons would effectively integrate into broken circuits, particularly in a hostile environment full of harmful proteins and inflammatory mediators. Again, regeneration and repair might be assisted by removing these hostile factors. Where stem cells could yield more immediate rewards is as models for studying the heterogeneity of AD. It is now possible to establish pluripotent stem-cell lines from skin cells of individual patients and to differentiate them into neurons or other brain cells. Comparing these cellular models might lead to the identification of patient-specific pathogenic pathways and modifier genes.

And prevention — is this feasible?

Preventative treatments would probably have to be started years, if not decades, before the first symptoms of AD appear. Treating people for such long periods would require drugs with minimal side effects and the ability to identify people with significant risk factors early on. We still do not have reliable early biomarkers for AD, although progress has been made (Fig. 2). An Alzheimer's Disease Neuroimaging Initiative is under way to determine if measuring changes in brain volume over time, glucose metabolism and amyloid deposition in the brain, and levels of Aβ and tau in the CSF, can identify people at high risk of developing the disease. Proteomics profiling of blood plasma has yielded protein 'fingerprints' that might be diagnostic and possibly even predictive of AD. Although whole-genome sequencing as a routine screening method is still quite a way off, it is relatively straightforward to screen for the known autosomal dominant AD mutations in the *APP, PS1* and *PS2* genes, and for the *APOE* ε4 gene.

So should everyone get genetic testing?

This depends on many factors, including one's family history, outlook on life and the desire to secure certain types of insurance. If early-onset AD runs in the family and one is contemplating having children, genetic testing for autosomal dominant AD mutations may be appropriate. In general, genetic testing for AD should be undertaken only with the advice of a physician and a genetic counsellor who are experienced in helping people weigh up all the risks and benefits. Many clinicians advise against genotyping for *APOE* ε4 and other susceptibility genes because these genes are primarily risk factors, and some carriers never develop AD. The lack of established preventative treatments also diminishes the value of knowing one's risks, although greater public awareness of AD risks might help to intensify the fight against this devastating condition.

Is there reason for hope?

Indeed there is. As we gain a greater understanding of the mechanisms of AD, drugs can be aimed at its root causes (not just at its symptoms). Several drugs with disease-modifying potential are already in advanced clinical trials (Table 1), and more are in the pipeline. Large-scale risk-factor profiling using genomic and proteomic screens may make it possible to identify subgroups of patients who stand to benefit from particular drugs or drug combinations. Zeroing in on the most responsive patient populations could make clinical trials more effective and guide long-term prevention strategies. ■

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The author declares competing financial interests. See online article for details.

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