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.

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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.