Review

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Alzheimer's Disease: Genes, Pathogenesis and Risk Prediction

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Abstract
With the aging of western society the contribution to morbidity of diseases of the elderly, such as dementia, will increase exponentially. Thorough preventative and curative strategies are needed to constrain the increasing prevalence of these disabling diseases. Better understanding of the pathogenesis of disease will enable development of therapy, prevention and the identification of high-risk groups in the population. Here, we review the genetic epidemiology of Alzheimer's disease, the most common cause of dementia in the western world. The search for genetic risk factors, though far from completed, has been of major importance for understanding the pathogenesis of Alzheimer's disease. Although effective therapy is still awaited, these findings have led to new avenues for the development of drugs.

Introduction

Although in the past century major progress has been made in unravelling the genetics of Alzheimer's disease (AD), many questions remain to be answered. The debates about its pathogenesis, diagnosis, therapy and prevention have not been settled yet. It is clear that AD is a complex multifactorial disorder. A great number of possible genetic risk factors have been investigated, but for most of these no clear association has been found [1]. The search for genetic risk factors has yielded three genes (amyloid precursor protein [2–5], presenilin-1 [6–10] and presenilin-2 genes [11, 12]) in which mutations were found which result in rare autosomal dominant forms of AD. One susceptibility gene (apolipoprotein E gene) has been identified which is a risk factor in the general population.

In this paper the prevalence and risk factors for AD are reviewed. The emphasis will be on the genes known to be involved in AD, their role in understanding the development of the disease, and their implications for diagnosis and clinical counselling.

Clinical Epidemiological Aspects of AD

Diagnosis and Prognosis

AD is the most common cause of dementia in the western world. The disease is clinically characterized by insidious onset and slow progression of cognitive decline. Most frequently, loss of short-term memory and impaired imprinting of new information are the presenting symptoms of AD. During the course of the disease, symptoms may further include disturbance of speech, poor judgment, personality change and deterioration of visuospatial skills, with preserved level of consciousness. Patients gradually lose the ability to be self-supportive, and even-

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tually they will become bedridden. Death usually occurs due to complications of immobility and malnutrition [13]. The average duration of AD is 8–10 years, although at old age survival may be shorter. Available therapeutic strategies (cholinesterase inhibitors) are not curative, but may halt the process of decline for half a year to 2 years in the early stages of the disease in a small number of patients [14].

The diagnosis is based on clinical examination and neuropsychological testing. These should yield no clues for systemic or other brain diseases capable of causing dementia, such as vascular dementia and subcortical dementia (NINCDS-ADRDA) [15]. Although the precision of the diagnosis has improved considerably with improvement of neuropsychological tests and neuroimaging, during life only a probable diagnosis can be made, with an accuracy of 80–90%. The definite diagnosis of AD is always based on histopathological findings in the brain [16]: neuritic plaques, neurofibrillary tangles and loss of neurons in hippocampus and cerebral cortex.

The neuritic plaques are composed of aggregations of β-amyloid, which are surrounded by dystrophic dendrites, microglia and astrocytes. These plaques are located preferentially in limbic and association cortices of the brain, areas important for memory and cognition.

Neurofibrillary tangles consist of intraneuronal aggregations of hyperphosphorylated tau. Tau is a protein that is normally present in adult human brain, where it exerts its function through stabilizing microtubules, which are essential for cell shape and support and intraneuronal transport. Hyperphosphorylated tau destabilizes the microtubule network within neurons. Due to subsequent neuronal dysfunction and deficits in neurotransmitters, normal brain function is impaired [17].

Prevalence of AD

The number of patients affected with AD (prevalence of disease) is remarkably stable in western society. The major determinant of the prevalence of disease is age. Less than 1% of the people aged 70 years or younger is affected with AD. But with each 5 years' increase in age the prevalence of AD doubles, until by age 90 years up to 30% is affected [18]. A large European follow-up study has shown that, especially at older age, women are more often affected than men [19, 20].

Although AD is considered to be a disease of the elderly, there are patients in whom first symptoms of AD may be present as early as at age 35 years. Frequently, a distinction is made between 'early-onset Alzheimer's disease' (EOAD) and 'late-onset Alzheimer's disease' (LOAD). The distinction is arbitrary, since clinical and pathological features are very similar in both groups. Age criteria for EOAD vary widely, but usually, when the age at onset of the disease is before 65 years of age, a patient will be diagnosed with EOAD [1].

Given its strong association with age, AD will be an increasing health care problem in the next decades. With the aging of western society, the number of patients is expected to increase exponentially. By the year 2025, over 22 million patients with dementia are expected around the world [21].

Risk Factors

AD has a complex etiology. Research in the past century has focused on many putative environmental factors that may either increase or decrease the risk of AD. These included age, smoking, maternal age at birth, head trauma, depression, thyroid disease, anti-inflammatory drugs, estrogen replacement therapy, alcohol, occupational exposure, aluminum, education and diet [22]. Findings regarding these risk factors have been inconsistent. Only increasing age and genetic predisposition are consistently correlated with the disease [1].

Perhaps most interesting from an epidemiological perspective is the finding that studies on vascular risk factors such as hypertension, diabetes mellitus, atherosclerosis, and high cholesterol have yielded promising results, showing an up to 2 times increased risk for AD [23–32]. The mechanism through which these vascular factors are associated with AD remains to be elucidated. It has been argued that these factors may be a primary cause of AD pathology [33]. An alternative explanation may be that vascular pathology is not a primary cause of AD, but rather that it accelerates the primary neurodegenerative process.

The findings of the relationship between vascular pathology and AD are in line with cross-cultural observations by Hendrie et al. [34]. They recently published results on differences in age-standardized annual incidence rates of AD in an industrialized versus a nonindustrialized country. A possible explanation for the decreased rate in the nonindustrialized country is the lower prevalence of cardiovascular disease in the nonindustrialized population. However, also differences in genetic makeup between populations may partly explain these findings. As discussed in the next chapter, genetic susceptibility is, in addition to increased age, the most important determinant of AD.

Genetics of AD

Familial Aggregation

As opposed to the difficulties encountered in finding environmental risk factors for AD, the genetic component of the disease has long been evident. Epidemiological studies have clearly shown that AD aggregates within families [35]. First-degree relatives of AD patients have a 3.5 times increased risk of developing AD. The relative risk increases with a decrease in the age at onset of the affected proband. In relatives of patients with an onset before age 70 years the risk of having AD is increased over 4 times [35]. Concordance rates of up to 80% have been found in monozygotic twins. In dizygotic twins concordance rates were 35% [36].

In few families an autosomal dominant pattern of inheritance can be recognized. A segregation analysis suggested an autosomal dominant model in less than 1% of 198 families with EOAD [37]. In LOAD, it is difficult to make a distinction between a dominant, recessive or additive model of inheritance [38]. In the majority of patients the etiology appears to fit a multifactorial model in which multiple genes and environmental factors interact [1].

Genes Involved in AD

Research on genetic determinants initially focused on families with an autosomal dominant pattern of inheritance. The first dominant mutation was found in the gene encoding the amyloid precursor protein *(APP)* on chromosome 21 [2–5]. Up until now, 32 families are known around the world with EOAD due to a dominant *APP* mutation (http://molgen-www.uia.ac.be/ADMutations/).

Besides *APP,* two homologous genes were identified, presenilin-1 *(PSEN-1)* at chromosome 14 and presenilin-2 *(PSEN-2)* at chromosome 1q31-q42, which account for families segregating AD as an autosomal dominant trait as well. So far, more than 80 mutations of the *PSEN-1* gene have been identified [6–10] (http://molgen-www.uia.ac.be/ADMutations/). Six mutations in *PSEN-2* are described [11, 12] (http://molgen-www.uia.ac.be/ADMutations/).

Frequency estimates of these mutations in EOAD patients are highly variable, ranging from less than 1 to 50% [e.g. 39–41]. Differences might be due to more or less stringent diagnostic criteria in the population under study (e.g. probable vs. autopsy-confirmed AD), different maximum age when considering early onset, and selection of study populations. A study population derived from a highly specialized neurological center is more likely to have an overrepresentation of cases with high familial aggregation. However, in a population-based sample [41] *APP* mutations were found in only 0.5% of all EOAD patients and accounted for only 0.005% of AD in the general population. Although mutations in *PSEN-1* are more common, they still only accounted for 6.5% of all EOAD patients (i.e. 0.065% of AD in the general population). Mutations in *PSEN-2* were seen in less than 1% of all EOAD patients, and less than 0.01% of the general population. Together, dominant mutations in *APP*, *PSEN-1* and *PSEN-2* occurred in only 0.075% of AD patients at the population level [41, 42]. Although these genes have a minor impact in the general population, for the individual carrier the risk is extremely high. Almost all carriers of these mutations express the disease. As EOAD is rare, risk estimates for carriers of these mutations approximate infinity.

In addition to the three autosomal dominant genes, a fourth gene (apolipoprotein E, *APOE*) was identified which is localized on chromosome 19 and has three common alleles coding for three different isoforms of the protein. The allele frequencies of this gene *(APOE)* are 0.08 for *APOE*2,* 0.77 for *APOE*3* and 0.15 for *APOE*4* in populations of European ancestry [42]. *APOE*4* is strongly associated with LOAD [43, 44] and EOAD [45]. Subjects homozygous for *APOE*4* have an almost 15 times increased risk of developing AD, but 50% will not develop the disease [46]. Subjects with only one *APOE*4* allele have a moderately increased risk (around 3 times) [47]. Although risks are moderately increased for *APOE*4* for the individual carrier, due to the fact that the allele is common *APOE*4* may explain 17% of the occurrence of AD in the general population [42]. Homozygosity for *APOE*4* contributes less than 2% to AD because of low prevalence of this genotype (0.0225). It is suggested that *APOE*4* regulates when rather than if the disease occurs [47, 48]. Due to a relatively earlier onset of LOAD in those homozygous for *APOE*4,* the influence of competing morbidity and mortality will be less, thereby enhancing the association between *APOE*4* homozygosity and LOAD.

Genes and the Pathogenesis of AD

The discovery of mutations in the genes involved in AD has been of great importance for the understanding of the biological mechanisms underlying AD. All causal mutations affect the normal metabolism of β-amyloid, suggesting that β-amyloid constitutes a central event in the pathogenesis of AD. β-Amyloid, or Aβ, is a peptide present under physiological circumstances in healthy subjects. Due to a mutation in any of the known AD genes,

the equilibrium between production and clearance of Aβ gets disturbed, resulting in accumulation of Aβ in the brain. Amyloid fibrils are formed and subsequently deposited into plaques. At present, the most likely hypothesis is that at first diffuse plaques are formed. These plaques can also be seen in healthy subjects. In AD patients several of these plaques may evolve into 'mature' neuritic plaques containing fibrillar aggregates, damaged neurons and activated glial cells in a cascade of pathological processes, eventually leading to profuse neuronal loss [49–57].

APP is a transmembrane protein that is widely expressed on the cell surface. Its functional properties are not clearly defined, but range from repair of vascular injury to mediation of growth and adhesion of neural and nonneural cells [53]. Recently it has been suggested that APP has a function in the regulation of nuclear transcription [58]. APP is cleaved into Aβ. The different mutations that have been found so far in the gene coding for APP are located at or near cleavage sites [40]. By abnormal cleavage of APP larger amounts of a longer version of Aβ are produced, called Aβ42 [59–62]. This longer version is more amyloidogenic and therefore aggregates more easily into plaques [63]. There is increasing evidence that Aβ42 may play a crucial role in the pathogenesis of AD.

The function of the presenilin proteins is unclear, but it has been shown that mutations in *PSEN* also lead to altered APP processing. Aβ42 levels are raised in brain, plasma and fibroblasts [64] of carriers of a *PSEN* mutation. Furthermore, in experiments with *PSEN*-transgenic mice and transfected cells higher Aβ42 levels are found as well [65–68].

In sporadic LOAD the pattern of Aβ accumulation is less evident. It has been suggested that accumulation is rather the result of impaired clearance of Aβ than of increased synthesis [57]. In carriers of the *APOE*4* allele, the predominant genetic risk factor in sporadic AD, APOE has increased affinity for Aβ and Aβ aggregates. Although the precise mechanism has not yet been elucidated, *APOE*4* is suggested to facilitate Aβ aggregation or to inhibit the elimination of the fibrillar aggregates [44, 69, 70].

Although a body of genetic evidence supports the Aβ cascade hypothesis and although it is the most comprehensive theory so far, the debates on this hypothesis have not been settled yet [50, 57, 71, 72]. Disagreement ranges from details within the Aβ hypothesis (e.g. that not the total amount of Aβ is important but rather the relative proportion of Aβ42) to the reverse hypothesis that Aβ accumulation is a compensatory mechanism to aging [73]. A finding difficult to explain has been that amyloid deposition does not seem to correlate very well with cognitive decline [50]. However, recent findings may have settled this argument by showing that Aβ plasma levels are elevated early in the course of the disease and are strongly related to cognitive decline, a finding in favor of the Aβ cascade hypothesis [74, 75].

While the Aβ hypothesis is being refined other pathogenic models are considered as plausible. These include hypotheses on the involvement of tau [76], on neuroplasticity [77], aging [72], oxidative stress [78], impaired cerebromicrovascular perfusion [79], inflammation [80] and lipid homeostasis [70].

Genetic Counselling and Risk Prediction

The identification of genes involved in AD has been a major breakthrough. Yet there is ongoing debate on their use in clinical counselling.

Given the fact that *APP, PSEN-1* and *PSEN-2* mutations have a virtually complete penetrance and that these mutations are not found in healthy age-matched subjects, one might argue that these mutations are useful for risk prediction and genetic counselling. But the known mutations are only present in a minority of cases. Although mutations can be found frequently in patient populations from highly specialized centers due to selection bias [81], these mutations are rare in the general population. Thus, for risk prediction and counselling, the absence of a known mutation should not be conclusive. Even if the underlying mutation is known in a family with an autosomal dominant form of AD, there is a strong argument against screening relatives at risk, because curative therapy and prevention are not yet at hand. An argument in favor of screening relatives at risk and those that already have dementia without a definite diagnosis might be to take away incertitude and allow for future plans, but screening should always be preceded by thorough counselling, taking into account ethical considerations.

Because of their low frequency, the mutations are not useful as a diagnostic tool for patients with early onset symptoms of dementia [39].

Also the use of *APOE* is limited in the clinical practice. *APOE*4* increases the susceptibility to AD, but the increase in risk is modest, especially in the heterozygous carriers of the *APOE*4* allele. As only 50% of the AD patients carry *APOE*4* and a substantial number of patients with other dementias show similar frequencies, *APOE*4* is not suitable for diagnostic purposes [82]. Even for subjects homozygous for the *APOE*4* allele there is still a 50% chance not to develop the disease [46]. Thus despite the

fact that *APOE* is a more important determinant of AD in the general population than *APP, PSEN-1* and *PSEN-2, APOE* is not suitable for risk prediction and counselling.

Considerations

The discovery of the dominant mutations in the *APP, PSEN-1* and *PSEN-2* genes in the families with autosomal dominant EOAD explains only a minor proportion of the disease in the general population. The clinical use is limited and awaits therapy and prevention. Nevertheless, genetic research has made a significant contribution to understanding the pathogenesis of the disease, even in sporadic patients. Genetic evidence is pointing towards a central role for amyloid metabolism in the etiology of AD. Due to the genetic evidence towards Aβ research focusing on Aβ has expanded impressively. Recently, promising evidence has been found in vaccination strategies with Aβ in mice, decreasing formation of Aβ [83] and enhancing cognition in mouse models [84–86]. Verification of these findings in man, combined with useful biomarkers, will be of tremendous importance in the prevention of this disabling disease. Recently, trials in humans were halted because of major side effects.

Meanwhile, other genetic and environmental factors should still be considered to fill the lacunae in our knowledge of AD. Better understanding of the neuropathological mechanisms underlying AD, whether based on genetic findings or on results of other kinds of scientific research, will without a doubt aid future therapeutic and preventive strategies.

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