

Alzheimer's disease

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Abstract

Alzheimer's disease is the most frequent type of dementia. It is due to neurons loss in different parts of the brain. It equally affects males and females, with a higher prevalence as age increases, particularly after the age of 60. Onset is marked with various alterations of the intellectual functions (recent memory, spatial and temporal orientation, language, use of objects, etc.) that progressively reduce the patient's autonomy. Familial forms are the minority and may be caused by a common genetic risk factor between relatives. The most important risk factor known is the genotype for the E apolipoprotein. Purely genetic (monogenic) forms occur much more rarely, usually before the age of 60, and are transmitted as autosomal dominant traits. Three genes have now been identified for these forms. They encode presenilins 1 and 2 and the amyloid precursor protein. Mutations in these genes directly or indirectly cause an increasing production of amyloid peptide, which accumulates in the brain. Among the 400,000 or so patients with Alzheimer's disease in France, fewer than 1% have monogenic forms. Various symptomatic treatments can be proposed to restore the cholinergic transmission, however they have no effect on the causes of the disease.

Key-words

Alzheimer's disease, dementia, Familial forms, E apolipoprotein, presenilins 1 and 2, amyloid precursor protein

Disease name and synonyms

Alzheimer's disease (AD)

Definition

Alzheimer's disease is an adult disorder whose prevalence increases with age, affecting 10 to 20% of the population aged over 80 years. It is a slowly progressive, neurodegenerative disease.

Clinical description

AD most commonly manifests as a selective memory loss of recent events associated with aphasia and apraxia. Patients suffering from AD may be unaware of these cognitive changes. Other signs may appear as the disease

progresses: psychiatric disorders, extrapyramidal syndrome, myoclonia, epileptic seizures. In the absence of effective therapy, patients lose progressively their autonomy and die after 5 to 15 years of disease evolution.

Definitive diagnosis is based on the neuropathological examination which reveals the hallmarks of the disease: senile plaques, formed by deposition of amyloid substance, and neurofibrillary tangles formed of abnormally phosphorylated Tau proteins. Complementary laboratory tests and imaging studies are mainly used to exclude other causes of dementia.

Etiology

The relationship between AD and heredity is complex. The disorder clearly is inherited as an autosomal trait in about 20% of early-onset forms (age of onset less than 60 years). In other forms, especially in late-onset forms, the occurrence of familial aggregation may be caused by genetic factors. Late-onset forms are by far the most frequent.

Three genes account for the rare, autosomal dominant early-onset forms: *APP* (encoding amyloid beta A4 precursor protein) located on chromosome 21, *presenilin 1* on chromosome 14, and *presenilin 2* on chromosome 1.

When the disease results from mutations in these genes, it is transmitted as an autosomal dominant trait with complete penetrance around the age of 60 years. The APP717 Val->Ile mutation is commonly found in the gene *APP*. The *presenilin 1* gene, the major causative gene in early-onset forms, is associated with various point mutations. The *presenilin 2* gene is rarely implicated. A fourth gene that has not yet been identified could account for early-onset forms in a few families. Mutations in the *presenilin 1* gene are sometimes responsible for atypical presentations including dementia with prominent frontotemporal features, or dementia with spastic paraplegia.

The e4 allele of the apolipoprotein E (ApoE), has been identified as risk factor in late-onset forms; it is only considered as a risk factor as carriers of one or two copies of the e4 allele will not necessarily develop AD, whilst not every patient with the disease is an e4 allele carrier. The relative risks of AD in e4 heterozygotes and e4/e4 homozygotes are approximately 2 or 3, and 7 to 9, respectively, compared with non carriers. No other genetic susceptibility factor has been demonstrated to be involved so far. However, several candidate regions, which contain yet unidentified genetic susceptibility factors, have been mapped in genome screens.

Molecular diagnosis

In families in which mutations in *APP*, *presenilin 1* or *2* have been characterized, diagnosis can be confirmed by DNA analysis.

In the late-onset forms, ApoE genotyping does not allow to confirm the diagnosis. Although the presence of one or two copies of allele e4 in patients presenting signs consistent with AD supports the hypothesis of the disease, it does not provide conclusive evidence for it. ApoE genotyping cannot be used to help confirm clinical diagnosis.

Presymptomatic diagnosis can only be carried out in a few AD families in which the disease is caused by mutations in *APP*, *presenilin 1* or *2* genes. Presymptomatic diagnosis should be only

considered for individuals at risk and clinically disease-free, who wish to know their genetic status for AD. In the absence of effective therapy, this type of diagnosis must only be carried in patients who have clearly thought through their reasons for wanting to know their status and who can cope with the results, even if unfavorable. Presymptomatic diagnosis should therefore only be envisaged when associated with a multidisciplinary management, extending over several months, similar to that proposed for Huntington's disease. Juveniles do not benefit from presymptomatic diagnosis.

Prenatal diagnosis

Prenatal diagnosis may be requested by couples in which one member carries mutations in *APP*, *presenilin 1* or *2* that are responsible for early-onset forms. A presymptomatic test has to have been previously carried out in the member at risk within the couple. If it does not lead to pregnancy interruption in case of an unfavorable result, the prenatal diagnosis is in effect the equivalent of a presymptomatic test in a juvenile.

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