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GENETests
Genetics IN Medicine

collaborative review

Genetic aspects of Alzheimer disease

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Alzheimer disease is the most common cause of dementia and represents a major public health problem. The neuropathologic findings of amyloid-β plaques and tau containing neurofibrillary tangles represent important molecular clues to the underlying pathogenesis. Genetic factors are well recognized, but complicated. Three rare forms of autosomal-dominant early-onset familial Alzheimer disease have been identified and are associated with mutations in amyloid precursor protein, presenilin 1, and presenilin 2 genes. The more common late-onset form of Alzheimer disease is assumed to be polygenic/multifactorial. However, thus far the only clearly identified genetic risk factor for Alzheimer disease is Apo lipoprotein E. The ϵ4 allele of Apo lipoprotein E influences age at onset of Alzheimer disease, but is neither necessary nor sufficient for the disease. The search continues for the discovery of additional genetic influences. ***Genet Med* 2008:10(4):231–239.**

Key Words: *Alzheimer, dementia, amyloid, neurogenetics*

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Clinical manifestations of Alzheimer disease

The clinical manifestation of Alzheimer disease (AD) is dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur.[1]

Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is 8–10 years, with a range from 1 to 25 years.

Establishing the diagnosis of Alzheimer disease

Establishing the diagnosis of Alzheimer disease relies on clinical-neuropathologic assessment.[1] Neuropathologic findings on autopsy examination remain the gold standard for diagnosis of AD. The clinical diagnosis of AD (before autopsy confirmation) is correct about 80–90% of the time.[2]

- Clinical signs: slowly progressive dementia
- Neuroimaging: gross cerebral cortical atrophy[3]
- Neuropathologic findings: microscopic extracellular amyloid-β (Aβ)-amyloid neuritic plaques, intraneuronal neu-

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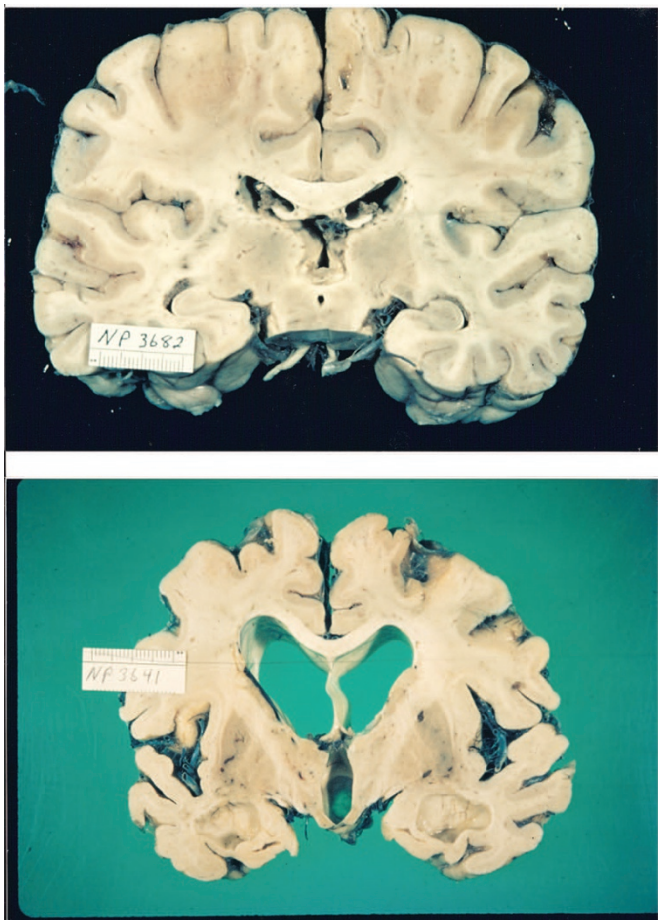

Fig. 1. Normal adult brain (top) compared with Alzheimer brain (bottom) showing marked diffuse cortical atrophy and ventricular enlargement.

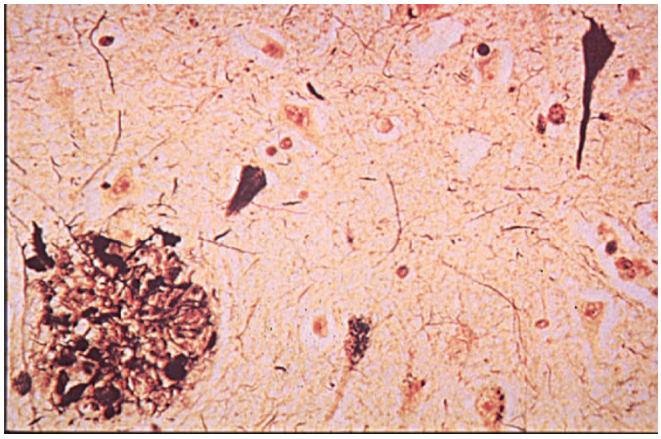

Fig. 2. Microscopic neuropathology of Alzheimer disease showing a neuritic plaque (lower left hand corner) and neurofibrillary tangles (upper right hand corner).

rofibrillary tangles, and amyloid angiopathy at postmortem examination (Figs. 1 and 2). The plaques should stain positively with Aβ-amyloid antibodies and negative for prion antibodies, which are diagnostic of prion diseases. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Guidelines for the quantitative assessment of these changes exist.[4,5] Aggregation of alpha-synuclein in the form of Lewy bodies may also be found in neurons in the amygdala.[6]

Table 1
Causes of Alzheimer disease

Cause	% of cases
Chromosomal (Down syndrome)	<1
Familial	~25
Late-onset familial (AD2)	15–25
Early-onset familial AD (AD1, AD3, AD4)	<2
Unknown (includes genetic/environment interactions)	~75

Differential diagnosis of Alzheimer disease

Differential diagnosis of AD includes other causes of dementia, especially treatable forms of cognitive decline, such as depression, chronic drug intoxication, chronic central nervous system infection, thyroid disease, vitamin deficiencies (especially B12 and thiamine), central nervous system angitis, and normal-pressure hydrocephalus.[1]

Other degenerative disorders associated with dementia, such as frontotemporal dementia, including frontotemporal dementia with parkinsonism-17, Picks disease, Parkinson disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), may also be confused with AD.[7]

Computerized tomography and magnetic resonance imaging are valuable for identifying some of these other causes of dementia, including neoplasms, normal-pressure hydrocephalus, frontotemporal dementia, and cerebral vascular disease.

Prevalence of Alzheimer disease

AD is the most common cause of dementia in North America and Europe, with an estimate of 4 million affected individuals in the United States.

The prevalence of AD increases with age. Mild memory loss is often called mild cognitive impairment. In many persons mild cognitive impairment is considered an early stage of AD.

The incidence of AD rises from 2.8 per 1000 person years in the 65–69 years age group to 56.1 per 1000 person years in the older than 90-year age group.[8] Approximately 10% of persons older than 70 years have significant memory loss and more than half of these individuals have AD. An estimated 25–45% of persons older than 85 years have dementia.

CAUSES

About 1–6% of all AD is early onset (before age 60–65 years) and about 60% of early-onset AD is familial, with 13% seeming to be inherited in an autosomal-dominant manner (Table 1).[9,10]

The distinction between early-onset familial AD (EOFAD, onset before age 60–65 years) and late-onset familial AD (onset after age 60–65 years) is somewhat arbitrary. Early-onset cases can occur in families with generally late-onset disease.[11]

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Table 2
Late-onset familial Alzheimer's disease: molecular genetics

Locus name	Gene symbol	Chromosomal locus	Protein name	Test availability
AD2	*APOE*	19q13.2	ApolipoproteinE	Clinical

Environmental causes

No environmental agents (e.g., head trauma, viruses, toxins, low education level) have been proven to be directly involved in the pathogenesis of AD. It is often speculated that late-onset AD is the result of unknown environmental factors acting on a predisposing genetic background.[12] Twin studies have implicated both genes and environment.[13]

Heritable causes

Chromosomal

Down syndrome. Essentially, all persons with Down syndrome (DS) (trisomy 21) develop the neuropathologic hallmarks of AD after 40 years. More than half of individuals with DS also show, if carefully observed or tested, clinical evidence of cognitive decline.[14] The presumed reason for this association is the lifelong overexpression of the *APP* gene on chromosome 21 encoding the amyloid precursor protein and the resultant overproduction of β-amyloid in the brains of persons who are trisomic for this gene.

The Aβ deposition in the brain may begin in the first decade of life in persons with DS.[15] AD was not noted clinically or pathologically in a 78-year-old woman with partial trisomy 21, who did not have an extra copy of the *APP* gene.[16] Two studies have found no association of Apo E genotype with age of onset of dementia in DS,[17,18] but one study did find an association of onset age with a polymorphism in the *APP* gene.[18] Schupf et al.[19] found an unexplained increased risk for AD in mothers younger than 35 years, who gave birth to children with DS.

Single gene. About 25% of AD is familial (i.e., two or more family members have AD). Familial cases seem to have the same clinical and pathologic phenotypes as nonfamilial cases (i.e., an individual with AD and no known family history of AD)[20,21] and are thus distinguished only by family history or by molecular genetic testing. A large volume of research on the molecular and genetic basis of AD has been summarized by Rosenberg,[22] Sleegers and van Duijn,[23] Nussbaum and Ellis,[24] Goedert and Spillantini,[25] and Roses and Saunders.[26]

Late-onset familial Alzheimer disease. Many families have multiple affected members, most or all of whom have onset of dementia after age 60 or 65 years (Table 2). Disease duration is typically 8–10 years, but ranges from 2 to 25 years. Investigations have supported the concept that late-onset AD is a complex disorder that may involve multiple susceptibility genes (reviewed and summarized by Kamboh,[27] Bertram and Tanzi,[28] Serretti et al.,[29] and Roses and Saunders[26]). Bertram et al.[30] have performed a meta-analysis on these data. The following information are currently available:

- Well-documented association of late-onset familial AD (FAD) with the *APOE* e4 allele. The *APOE* e4 allele, by unknown mechanisms, seems to affect age of onset by shifting the onset toward an earlier age.[31,32]
- Several other potential genes are under investigation:
  - *SORL1* on chromosome 11q23, a protein involved with amyloid precursor protein (APP) trafficking[33]
  - *A2M* on chromosome 12[34–37]
  - *GST01* and *GST02* on chromosome 10[38]
  - *GAB2* on chromosome 11q14 interacting with the *APOE* e4 allele[39]
- Several other potential loci are under investigation on the following chromosomes:
  - 12[40–43]
  - 10[44–48]
  - 2q, 9p, and 15q[49,50]
  - 19p13[51]
  - 7q36[52]
  - 9q22 (*UBQLN1*)[53–56]
- Studies of late-onset AD in a genetically isolated Dutch population have suggested linkage of AD to markers on chromosome 1q22, 3q23, 10q22, and 11q25.[57]

Early-*onset familial Alzheimer disease*

- Clinical features: EOFAD refers to families in which multiple cases of AD occur with the mean age of onset usually before age 65 years, although some studies have used age 60 or 70 years. Age of onset is usually in the 40s or early 50s, although onset in the 30s and early 60s has been reported. Campion et al.[10] found a prevalence of early-onset AD in the general population of 41.2 per 100,000 persons at risk (ages 40–59 years). Sixty-one percent of these individuals with early-onset AD had a positive family history, and 13% met stringent criteria for autosomal-dominant inheritance (i.e., affected individuals in three generations). EOFAD cannot be clinically distinguished from nonfamilial AD except on the basis of family history and age of onset. The dementia phenotype is similar to that of late-onset AD, sometimes with a long prodrome.[58–60]
- Molecular genetics: At least three subtypes of EOFAD (AD1, AD3, and AD4) have been identified based on the causative gene. The relative proportion of each subtype and the causative genes are summarized in Table 3.[10,61–63] The APP is cleaved by alpha- and gamma-secretases to form the A beta-peptide, which is the primary component of the extracellular amyloid plaque deposited in AD (Fig. 3). Presenilin 1 (PS1) is part of the gamma-secretase complex (and PS2 is a close homolog of PS1). Thus, the three primary genes associated with EOFAD are all related to APP and A beta-amyloid molecular biology. It is likely that other genes will be identified as a cause of EOFAD because kindreds with autosomal-dominant FAD with no known mutations in presenilin 1 (*PSEN1*), *PSEN2*, or *APP* have been described.[63,64]

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Table 3
Early-onset familial Alzheimer disease (EOFAD): molecular genetics

Locus name	Proportion of EOFAD	Gene symbol	Chromosomal locus	Protein name	Test availability
AD3	20–70%	*PSEN1*	14q24.3	Presenilin-1	Clinical
AD1	10–15%	*APP*	21q21	Amyloid beta A4 protein	Clinical
AD4	Rare	*PSEN2*	1q31-q42	Presenilin-2	Clinical

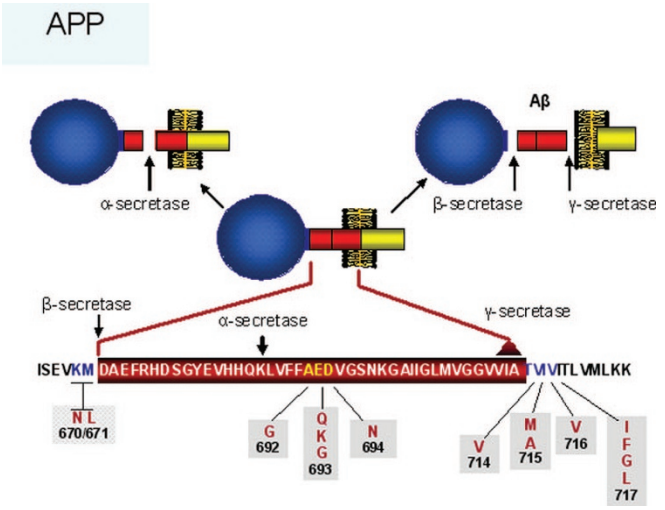

Fig. 3. Molecular aspects of the APP gene and protein showing the sites of cleavage by α, β, and γ secretases, production of the Aβ peptide (upper right), and sites of several disease causing mutations (bottom line).

Table 4
Percent of *APOE* genotypes in controls and individuals with AD

APOE genotype	Normal controls ($n = 304$)	All individuals with AD ($n = 233$)	Individuals with AD and positive family history of dementia[a] ($n = 85$)
e2/e2	1.3%	0%	0%
e2/e3	12.5%	3.4%	3.5%
e2/e4	4.9%	4.3%	8.2%
e3/e3	59.9%	38.2%	23.5%
e3/e4	20.7%	41.2%	45.9%
e4/e4	0.7%	12.9%	18.8%

Modified from Jarvik G, Larson EB, Goddard K, Schellenberg GD, et al. Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *Am J Hum Genet* 1996;58:191–200.
[a]Most families would be considered to have late-onset familial AD.

Unknown causes

Individuals with nonfamilial AD meet the diagnostic criteria for AD and have a negative family history. Onset can be anytime in adulthood. The exact pathogenesis of the disease is unknown. A common hypothesis is that nonfamilial AD is multifactorial and results from a combination of aging, genetic predisposition, and exposure to one or more environmental agents, such as head trauma, viruses, and/or toxins[65] although no environmental agents have been proven to be directly involved in the pathogenesis of AD.

EVALUATION STRATEGY

Family history

A three-generation family history with close attention to the history of individuals with dementia should be obtained. For each affected individual, the age of onset of dementia should be noted. Generally, individuals with onset before age 65 years are considered to have early-onset AD and those with onset after age 65 years are considered to have late-onset AD. Medical records of affected family members, including reports of neuroimaging studies and autopsy examinations, should be obtained.

- The diagnosis of EOFAD is made in families with multiple cases of AD in which the mean age of onset is before age 60–65 years.
- The diagnosis of late-onset FAD is made in families with multiple cases of AD in which the mean age of onset is after age 60–65 years.

Molecular genetic testing

Late-onset familial AD

The association of one or two copies of the *APOE* allele e4 (i.e., genotypes e2/e4, e3/e4, e4/e4) with late-onset AD is well documented (Table 4).[32,66,67]

- The association between *APOE* e4 and AD is greatest when the individual has a positive family history of dementia. The last column of Table 4 largely represents late-onset familial AD.
- The strongest association between the *APOE* e4 allele and AD, relative to the normal control population, is with the e4/e4 genotype. That genotype occurs in about 1% of the normal control population and in nearly 19% of the familial AD population.
- In individuals who have the clinical diagnosis of AD, the probability that AD is the correct diagnosis is increased to about 97% in the presence of the *APOE* e4/e4 genotype.[68]
- The increased risk of AD associated with one *APOE* e4 allele or two *APOE* e4 alleles is also found in African-Americans[69] and Caribbean Hispanics.[70]
- Approximately 42% of persons with AD do not have an *APOE* e4 allele. Thus, *APOE* genotyping is not specific for AD. The absence of an *APOE* e4 allele does not rule out the diagnosis of AD[2].
- Breitner et al.[71] have estimated lifetime risks for developing AD based on gender and *APOE* genotype (see Testing of At-risk Asymptomatic Individuals under Genetic Counseling).

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The usefulness of *APOE* genotyping in clinical diagnosis and risk assessment remains unclear (Statements and Policies Regarding Genetic Testing).

- Although the presence of one *APOE* e4 allele or two *APOE* e4 alleles is neither necessary nor sufficient to establish a diagnosis of AD, *APOE* genotyping may have an adjunct role in the diagnosis of AD because a large proportion of individuals with one *APOE* e4 allele or two *APOE* e4 alleles who are demented have been found to have neuropathologic confirmation of AD at autopsy.[2,66,72,73]
- In contrast, *APOE* genotyping was not found to be of significant diagnostic use in identifying AD in a community-based sample with late-onset dementia.[74]

There is some evidence that the *APOE* e2 allele may have a protective effect in regard to risk for AD (Table 4).

Another way to look at this association between AD and an *APOE* e4 allele is with *APOE* e4 allele frequencies (Table 5).

Early-onset familial AD

The three known subtypes of EOFAD, called AD3, AD1, and AD4[74,75] can only be distinguished by molecular genetic testing (Table 3). Genetic testing of individuals who are simplex cases (i.e., a single occurrence of early-onset AD in a family) is controversial and should be undertaken in the context of formal genetic counseling.[76] A small proportion (<5%) of such cases will have a mutation in PS1.

GENETIC COUNSELING

Mode of inheritance

Because AD is genetically heterogeneous, genetic counseling of persons with AD and their family members must be tailored to the information available for that family. AD is usually considered polygenic and multifactorial. EOFAD is inherited in an autosomal-dominant manner.

Risk to family members—late-onset nonfamilial Alzheimer disease

Genetic counseling for people with nonfamilial AD and their family members must be empiric and relatively nonspecific. It should be pointed out that AD is common and that the overall lifetime risk to any individual of developing dementia is approximately 10–12%.

First-degree relatives of a person with AD have a cumulative lifetime risk of developing AD of about 15–30%, which is typically reported as a 20–25% risk.[77,78] This risk is about 2.5 times that of the background risk (~27% vs. 10.4%).[79,80]

Disagreement exists as to whether the age of onset of the affected person changes the risk to first-degree relatives. One study found that early-onset AD increased the risk,[78] whereas another study did not.[77]

The number of additional affected family members probably increases the risk to close relatives, but the magnitude of that increase is unclear unless the pattern in the family is characteristic of autosomal-dominant inheritance. Having two, three, or more affected family members probably raises the risk to other first-degree relatives in excess of that noted above for nonfamilial cases, although the exact magnitude of the risk is not clear. Heston et al.[81] found a 35–45% risk of dementia in individuals who had a parent with AD and a sib with onset of AD before age 70 years. Jayadev et al.[82] also report data suggesting that offspring of parents with conjugal AD (i.e., both parents affected) had an increased risk of dementia.

Risk to family members—early-onset familial Alzheimer disease

Many individuals diagnosed as having early-onset AD have another affected family member, although family history is negative 40% of the time.[10] Family history may be "negative" because of early death of a parent, failure to recognize the disorder in family members, or, rarely, a de novo mutation. The risk to sibs depends upon the genetic status of the affected proband's parent. If one of the proband's parents has a mutant allele, then the risk to the sibs of inheriting the mutant allele is 50%. Individuals with EOFAD (and a mutation in *APP*, *PS1*, or *PS2*) have a 50% chance of transmitting the mutant allele to each child. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related genetic counseling issues

Use of APOE genotyping for predictive testing

In contrast to the use of *APOE* testing as an adjunct diagnostic test in individuals with dementia, there is general agreement that *APOE* testing has limited value used for predictive testing for AD in asymptomatic persons. Data suggest that a young asymptomatic person with the *APOE* e4/e4 genotype may have an approximately 30% lifetime risk of developing AD.[83] Further refinement of this risk reveals that women with an *APOE* e4/e4 genotype have a 45% probability of developing AD by age 73 years, whereas men have a 25% risk.[71] These risks are lower—and the likely age of onset later—for persons with only one *APOE* e4 allele (peak age 87 years) or no *APOE* e4 allele (peak age 95 years). These estimates are not generally considered clinically useful; however, a research study to assess the potential use of *APOE* testing in relatives of individuals with late-onset AD is under way.[79,84]

Table 5
APOE allele frequencies in controls and individuals with AD

APOE allele	Normal controls ($n = 304$)	All individuals with AD ($n = 233$)	Individuals with AD and positive family history of dementia[a] ($n = 85$)
e2	9.0%	3.9%	5.9%
e3	76.5%	60.5%	48.2%
e4	13.7%	35.6%	45.9%

Modified from Jarvik G, Larson EB, Goddard K, Schellenberg GD, et al. Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *Am J Hum Genet* 1996;58:191–200.
[a]Most families would be considered to have late-onset familial AD.

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Down syndrome

Family members of persons with DS are not at increased risk for AD.

Testing of at-risk asymptomatic EOAD family members

Testing of at-risk asymptomatic adults

Testing of asymptomatic adults at risk for EOFAD caused by mutations in the *PSEN1*, *PSEN2*, or *APP* gene is available clinically. Testing results for at-risk asymptomatic adults can only be interpreted after an affected family member's disease-causing mutation has been identified. It should be remembered that testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing.

Preliminary results have shown that although relatively few family members choose such testing, they usually cope well with the results, which can affect personal relationships and emotional well-being.[85] However, significant depression after such testing has been reported.[86]

Testing of at-risk individuals during childhood

Consensus holds that individuals at risk for adult-onset disorders should not have testing during childhood in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications.

Prenatal testing

Prenatal diagnosis for pregnancies at increased risk for mutations in the *PSEN1* gene is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15–18 weeks' gestation or chorionic villus sampling at about 10 to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

No laboratories offering molecular genetic testing for prenatal diagnosis of EOFAD caused by *APP* or *PSEN2* mutations are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified.

Requests for prenatal diagnosis of adult-onset diseases are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. Preimplantation diagnosis has been reported in a mother with an *APP* mutation.[87,88]

MANAGEMENT

Treatment of manifestations

The mainstay of treatment for AD is necessarily supportive and each symptom is managed on an individual basis.[1] In general, affected individuals eventually require assisted living arrangements or care in a nursing home.

Although the exact biochemical basis of AD is not well understood, it is known that deficiencies of the brain cholinergic system and of other neurotransmitters are present. Drugs that increase cholinergic activity by inhibiting acetylcholinesterase produce a modest but useful behavioral or cognitive benefit in some affected individuals. The first such drug was tacrine; however, this agent is also hepatotoxic. Newer such drugs with similar pharmacologic action, such as Aricept® (donepezil),[89–91] Exelon® (rivastigmine),[92] and galantamine,[93–95] are not hepatotoxic.

Memantine, an NMDA receptor antagonist, has shown some effectiveness in the treatment of moderate to severe AD.[96–99]

Antidepressant medication may improve associated depression.

Therapies under investigation

Treatment trials evaluating use of anti-inflammatory agents (NSAIDs), estrogens, nerve growth factors, ginkgo biloba, statins, beta-site cleaving enzyme (BACE) inhibitors, and antioxidants are under way or recently reviewed.[100–102]

Other

Vitamins and other over-the-counter medications have been used in the treatment of AD.[103]

Some, but not all, reports suggest that affected individuals taking 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase inhibitors for hypercholesteralemia have a reduced incidence of dementia.[104–106]

Immunization of an AD mouse model with β-amyloid has attenuated the AD pathology and stimulated the search for a possible vaccination approach to the treatment of human AD.[107] A human trial of this approach was halted because of encephalitis in a few subjects.[108–110] Alternative approaches to immunization therapy have been proposed.[111]

Thus far, treatment of symptomatic AD with estrogens has not proven beneficial.[112,113]

Genetics clinics

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources.

Support groups

Support groups have been established for individuals and families to provide information, support, and contact with

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other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

SUMMARY

Disease characteristics

AD is characterized by dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur. Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is 8 to 10 years, with a range from 1 to 25 years. About 25% of all AD is familial (i.e., two or more persons in a family have AD) of which about 95% is late-onset (after age 60–65 years) and 5% is early-onset (before age 65 years).

Diagnosis/testing

Establishing the diagnosis of AD relies upon clinical-neuropathologic assessment. Neuropathologic findings of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles remain the gold standard for diagnosis. The clinical diagnosis of AD, based on signs of slowly progressive dementia and findings of gross cerebral cortical atrophy on neuroimaging, is correct about 80–90% of the time. The association of the *APOE* e4 allele with AD is significant; however, *APOE* genotyping is neither fully specific nor sensitive. *APOE* genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals and a limited role at this time in predictive testing of asymptomatic individuals. Three forms of EOFAD caused by mutations in one of three genes (*APP*, *PSEN1*, and *PSEN2*) are recognized. Molecular genetic testing of the three genes is available in clinical laboratories.

Management

Treatment is supportive. Each symptom is managed on an individual basis. Assisted living arrangements or care in a nursing home is usually necessary. Drugs that increase cholinergic activity by inhibiting acetylcholinesterase produce a modest but useful behavioral or cognitive benefit in some affected individuals. Antidepressant medication may improve associated depression. An NMDA receptor antagonist is also FDA approved.

Genetic counseling

Because AD is genetically heterogeneous, genetic counseling of persons with AD and their family members must be tailored to the information available for that family. It should be pointed out that AD is common and that the overall lifetime risk for any individual of developing dementia is approximately 10–12%. Genetic counseling for people with nonfamilial AD and their family members must be empiric and relatively nonspecific. First-degree relatives of a simplex case of AD (i.e., single occurrence in a family) have a cumulative lifetime risk of developing AD of about 15–30%, which is typically reported as a 20–25% risk. This risk is about 2.5 times that of the background risk (~27% vs. 10.4%). In contrast, EOFAD with mutations in *APP*, *PS1* or *PS2* is inherited in an autosomal-dominant manner.

RESOURCES

Alzheimer's Association National Headquarters, 225 North Michigan Avenue Fl 17, Chicago, IL 60601-7633, Phone: 800-272-3900, 312-335-8700, Fax: 312-335-1110, E-mail: info@alz.org, www.alz.org.

Alzheimer's Disease Education and Referral Center, PO Box 8250, Silver Spring, MD 20907-8250, Phone: 800-438-4380; 301-495-3334, Fax: 301-495-3334, E-mail: adear@ alzheimers.org, www.alzheimers.org.

National Library of Medicine Genetics Home Reference, Alzheimer Disease.

NCBI Genes and Disease, Alzheimer Disease.

National Institute on Aging, Building 31, Room 5C27, 31 Center Drive MSC 2292, Bethesda, MD 20892, Phone: 301-496-1752, E-mail: karpf@nia.nih.gov, www.nia.nih.gov.

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