Dementia

Key Points

Genetics

- A variant of the apolipoprotein E gene, called ApoE ε4, is associated with an increased likelihood of developing Alzheimer disease (AD).
- Some experts have suggested testing for ApoE gene variants as part of the diagnostic workup of dementia, but others disagree about the usefulness of this test. Such testing may reveal unwanted genetic information for a patient's family members.
- Several expert panels have recommended against ApoE genotyping as a means of establishing the risk for AD in asymptomatic people.
- The effect of the ApoE genotype may vary by ethnicity, gender, and age.

Ethics

- Social implications of genetic testing for AD can be significant.

Learning Objectives

Participants will be able to:

- Understand the contribution of ApoE genotype to risk of AD;
- Describe the clinical and social implications of ApoE genotyping.

Family History Issues

First-degree relatives of a person with AD have a cumulative lifetime risk of about 20-25%, compared to the average risk of 10-12%. Risk of AD also increases with age and is significantly elevated among those who live beyond the average lifespan; for example, the prevalence of AD in people older than 85 years has been estimated at 25-50%.
Red Flags

The dementia seen in AD typically begins with subtle failure of memory and slowly becomes more severe. Common symptoms include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations.

Case 14. Suspected Dementia in an 80-Year-Old Woman

Admission. You are the attending physician for an inpatient team. The team admitted an 80-year-old woman, Mrs. P, with acute confusion who is found by labs done in the ER to have a UTI. She improves slightly on antibiotic therapy but continues to be confused. A more complete history is obtained from her son who reports that she has been failing for some years, with progressive confusion and inability to manage her own affairs. A mini-mental status examination indicates dementia. The resident has found no focal abnormalities on neurologic examination except for mildly impaired hearing bilaterally. After confirmation of these physical examination findings, further workup is discussed. The team orders basic blood chemistries, CBC, thyroid studies, liver function tests, vitamin B12 levels, and a head CT to rule out structural brain abnormalities. The patient's UTI resolved with treatment. She was discharged home.

Second visit. Mrs. P returns with a caretaker to see the resident in continuity clinic a week later. Lab studies and CT are normal. The resident has learned that the patient's father, an immigrant from Sweden, developed AD at age 78 years. On the basis of an article in the New England Journal of Medicine [Mayeux et al 1998], the resident has ordered ApoE genotyping. He did so in part because the family history suggests a genetic etiology and in part because the presence of an ApoE ε4 allele will increase the likelihood that the patient's dementia is due to AD, while its absence will make AD less likely. You find out after this visit that the test results are available and that Mrs. P is homozygous for the ApoE ε4 allele.

Third visit. Mrs. P is accompanied by her son, Mr. P, for follow-up. The results of the workup are discussed. The ApoE ε4 test result is explained as a finding consistent with a genetic predisposition to AD, although there is no other family history of AD. Mr. P asks whether this test could indicate...
whether he too will develop AD.

**Clinical Care Issues**

**Identifying the cause of dementia**

The initial workup focused on treatable causes of dementia. The tests used in this case represent a common approach to workup for treatable causes of dementia, although the specific tests ordered may vary based on a particular patient's presentation or co-existing medical problems. Other causes of dementia that should be considered include exposure to drugs or toxins and cerebrovascular disease. In addition to dementia, depression and delirium need to be considered as an explanation for her altered mental status [Ramsdell et al 1990]. Delirium may be caused by factors such as drug reactions, metabolic disorders, systemic illnesses (e.g., infection), cerebrovascular diseases and other CNS disease. Alzheimer disease accounts for about half of cases of dementia that lack other neurologic findings, with most of the remainder due to cerebrovascular disease.

**ApoE genotyping for Alzheimer disease**

Three common variants of apolipoprotein E (ApoE) occur: ApoE ε2, ApoE ε3, and ApoE ε4. Epidemiological studies have documented ApoE ε4 as a risk factor for AD, especially among those with a family history of AD. The presence of ApoE ε2 appears to reduce the risk for AD.

In studies of white patients with suspected AD, the presence of one or more ApoE ε4 alleles has been shown to increase the likelihood of the diagnosis [Tsuang et al 1999]. Thus, if Mrs. P has an ApoE ε4 allele, the probability is higher that her dementia is due to AD. The positive and negative predictive values of ApoE genotyping (for the presence of one or more ε4 alleles) are estimated to be 88% and 40%, respectively [Tsuang et al 1999]. These predictive values are not sufficiently high to either rule in or rule out AD as a cause of the patient's dementia, and thus would not change the diagnostic workup. In other words, presence of two ApoE ε4 alleles (i.e., homozygous genotype) is not diagnostic for AD, and therefore does not eliminate the need to evaluate the patient for other causes of dementia, particularly those that are treatable. Therefore, ApoE genotyping has not been proven useful for diagnostic purposes in population-based testing [Tsuang et al 1999].
Risk Assessment

Mr. P has asked whether his mother's genetic test results indicate an increased risk of AD for him. Two factors increase Mr. P's risk of AD: his family history and his ApoE genotype. On the basis of family history alone, his risk of AD is higher than average (Table 1). In addition, we know that he must have at least one copy of the ApoE ε4 allele, because his mother is homozygous for ApoE ε4. When family history and ApoE status are taken together, his risk of developing AD is at least two to three times higher than average (Tables 1 and 2). He also has a higher risk of developing AD before age 65 years.

It is not clear that this risk information provides any benefit to Mr. P. His mother's dementia and known ApoE status do not allow him to anticipate whether he will develop AD and, if so, at what age. No treatment is available to prevent AD in individuals heterozygous or homozygous for ApoE ε4.

Table 1. Risk of AD with Positive Family History

<table>
<thead>
<tr>
<th>Risk Assessed</th>
<th>Definition of &quot;Positive Family History&quot;</th>
<th>Odds Ratio (95% Confidence Interval) for Positive Family History vs Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD before age 65, in people with no ApoE ε4 allele [van Duijn et al 1994]</td>
<td>Report of dementia in first-degree relative; history confirmed by another relative</td>
<td>2.9 (1.6-5.6)</td>
</tr>
<tr>
<td>AD before age 65, in people with no ApoE ε4 allele [Jarvik ey al 1996]</td>
<td>Report by subject or surrogate of parent or sibling with progressive memory problems interfering with daily activities</td>
<td>2.7 (1.8-4)</td>
</tr>
<tr>
<td>AD after age 85 [Payami et al 1997]</td>
<td>Report by subject or surrogate of parent or sibling with AD, dementia, or progressive memory loss</td>
<td>3.8 (0.87-16.5)</td>
</tr>
</tbody>
</table>
### Table 2. Odds Ratio for Alzheimer Disease vs Controls for each Genotype, Compared to the ε3/ε3 Genotype (whites)

<table>
<thead>
<tr>
<th>ApoE Genotype</th>
<th>Odds Ratio (95% Confidence Interval)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε4/ε4</td>
<td>14.9 (10.8-20.6)</td>
</tr>
<tr>
<td>ε4/ε3</td>
<td>3.2 (2.8-3.8)</td>
</tr>
<tr>
<td>ε4/ε2</td>
<td>2.6 (1.6-4.0)</td>
</tr>
<tr>
<td>ε3/ε2</td>
<td>0.6 (0.5-0.8)</td>
</tr>
<tr>
<td>ε2/ε2</td>
<td>0.6 (0.2-2.0)</td>
</tr>
</tbody>
</table>

1. Data obtained from meta-analysis by Farrer et al 1997

### Effects of ethnicity, age and gender

Some studies suggest that ApoE status is more predictive in whites than in Hispanics or African Americans, and one report found a stronger association between ApoE ε4 and AD among Japanese subjects than among white subjects (see meta-analysis by Farrer et al 1997). Age and gender differences have also been observed in the effect of ApoE ε4 on AD risk, with stronger effects observed in females [Jarvik et al 1996; Farrer et al 1997] and among individuals under age 70 years [Farrer et al 1997].

### Genetic Counseling and Testing

Mr. P already knows he must have inherited one ApoE ε4 allele from his mother, but he may be concerned about whether he also inherited an ApoE ε4 allele from his father. The laboratory testing is available but is of uncertain clinical utility. Position statements against the predictive use of ApoE genetic testing have been published [ACMG/ASHG 1995, Post et al 1997]. Experts have cited two arguments against the predictive use of ApoE genetic testing:

- AD occurs in the absence of ApoE ε4 and some individuals homozygous for ApoE ε4 will not develop AD;
- There are no specific measures to prevent AD.

### Interventions
Preventive care

No measures have been proven to reduce the risk of developing AD or stop the progression of the disease.

Other clinical management of patients with AD

The mainstay of treatment is supportive. Each symptom is managed on an individual basis. In general, affected individuals eventually require assisted living arrangements or care in a nursing home. In many areas, courses and support groups are available for family members and caregivers.

There is no proven medical therapy for AD. Use of drugs that increase cholinergic activity by inhibiting acetylcholinesterase produces a modest but useful behavioral or cognitive benefit in a minority of patients. Some studies suggest short-term benefit with tacrine, donepezil, rivastigmine, or similar drugs, but such therapy remains controversial [Qizilbash et al 1998]. The magnitude of benefit may be greater in clinical trials than in practice. The effect of ApoE status on response to tacrine has been evaluated in a few small studies with conflicting results [Farlow et al 1998, MacGowan et al 1998, Rigaud et al 2000].

Treatment trials evaluating use of other factors, such as anti-inflammatory agents (NSAIDs), estrogens, nerve growth factors, lipid lowering agents, ginkgo, and Vitamin E are underway. Thus far, no effective treatments have been identified.

Ethical/Legal/Social/Cultural Issues

Psychosocial effects of ApoE testing

In deciding whether to perform ApoE genotyping on a patient with dementia, physicians and patients should discuss the effects of learning this information. While genotyping Mrs. P may seem reasonable because it could help clarify the cause of her dementia, the genetic test results could reveal unwanted information about the genetic status of her children or other family members. Anxiety or other adverse psychological effects could result from having this information. Since knowledge of Mrs. P's genotype has little diagnostic value, the potential risk or burden to family members may outweigh any benefit of testing Mrs. P.
Case 14. Dementia

Risk of insurance and employer discrimination

Identifying an increased risk of AD in an asymptomatic person through genetic testing could cause harm through discrimination. For example, if Mr. P were seeking a promotion and his employer knew of his increased risk for AD, that information could conceivably influence the promotion decision. Knowledge of an increased risk of AD could also make it harder for Mr. P to obtain life insurance or individually-rated health insurance. These possibilities underscore the concerns of policymakers about the importance of preserving the confidentiality of predictive genetic information and preventing its inappropriate use in insurance and employment decisions [Hudson et al 1995, Lapham et al 1996].

Resources

- Alzheimer's Association National Headquarters
  919 North Michigan Avenue, Suite 1000
  Chicago, IL 60611-1676
  Phone: 800-272-3900; 312-335-8700
  Fax: 312-335-1110
  Email: info@alz.org

- Alzheimer's Education and Referral Center
  PO Box 8250
  Silver Springs, MD 20907-8250
  Phone: 800-438-4380
  Email: adebianp@alz.org

- National Institute on Aging
  Building 31, Room 5C27
  31 Center Drive, MSC 2292
  Bethesda, MD 20892
  Phone: 301-496-1752

- National Library of Medicine Genetics Home Reference: Alzheimer Disease

- NCBI Genes and Disease Webpage: Alzheimer Disease

References


Case 14. Dementia


