

Early-onset Familial Alzheimer's Disease (EOFAD)

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Basic Information

- Early-onset familial Alzheimer's disease (EOFAD) is inherited in an autosomal dominant manner.
- Most individuals diagnosed as having EOFAD have had an affected parent. Because the onset of EOFAD is typically in early adulthood and the progression is rapid, affected parents are not alive at the time of diagnosis of their children.
- Occasionally, neither parent is identified as having had the disease, but a second-degree relative (e.g., an uncle, aunt, and/or grandparent) has or had EOFAD.

The Ten Cardinal Signs of Early Onset Familial Alzheimer's

- 1) MEMORY LOSS THAT DISRUPTS DAILY LIFE
- 2) CHALLENGES IN PLANNING OR SOLVING PROBLEMS
- 3) DIFFICULTY COMPLETING FAMILIAR TASKS AT HOME, AT WORK, OR AT LEISURE
- 4) CONFUSION WITH TIME OR PLACE
- 5) TROUBLE UNDERSTANDING VISUAL IMAGES AND SPATIAL RELATIONSHIPS
- 6) NEW PROBLEMS WITH WORDS IN SPEAKING OR WRITING
- 7) MISPLACING THINGS AND LOSING THE ABILITY TO RETRACE STEPS
- 8) DECREASED OR POOR JUDGMENT
- 9) CHANGES IN MOOD AND PERSONALITY
- 10) WITHDRAWAL FROM WORK OR SOCIAL ACTIVITIES

Classical Diagnostic Methods

EOFAD is diagnosed in families with multiple affected individuals with mean age of onset before 65 years and/or with a documented disease-causing mutation in one of the genes known to be associated with EOFAD.

The three clinically indistinguishable subtypes of EOFAD based on the underlying genetic mechanism are: Alzheimer disease type 1 (AD1), caused by mutations in *APP* (10%-15% of EOFAD); Alzheimer disease type 3 (AD3), caused by mutations in *PSEN1*, (30%-70% of EOFAD); and Alzheimer disease type 4 (AD4), caused by mutations in *PSEN2* (<5% of EOFAD). Molecular genetic testing for *PSEN1*, *PSEN2*, and *APP* is available on a clinical basis.

Diagnoses can also be made by neuro-imaging studies of cerebral cortical atrophy.

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- Presenilin-1, nicastrin, APH-1 and PEN-2 form a functional γ -secretase complex, located in the plasma membrane and endoplasmic reticulum (ER) of neurons. The complex helps in generating the amyloid β -peptide. This involves an initial cleavage of the amyloid precursor protein (APP) by an enzyme called BACE (or γ -secretase). The γ -secretase then liberates $A\beta$, as well as an APP cytoplasmic fragment, which may move to the nucleus and regulate gene expression. Mutations in presenilin-1 that cause early-onset Alzheimer's disease enhance γ -secretase activity and $A\beta$ production, and also perturb the ER calcium balance. Consequent neuronal degeneration may result from membrane-associated oxidative stress, induced by aggregating forms of $A\beta$ (which create $A\beta$ plaques), and by the perturbed calcium balance.

Exigence of Finding EOFAD Treatments

- More than 5 million Americans are living with EOFAD.
- One in eight people 65 and older have EOFAD, and unless scientists discover a way to delay EOFAD some 7.7 million people are expected to have the disease by 2030.
- By 2050, that toll could reach 16 million.

Available Treatments for EOFAD

- There is no known cure for Alzheimer's disease, but some medications may have benefit in preserving independence for a period of time, and prolonging the time that the patient can be managed at home. These include:
 - · Anticholinesterases - Donepezil, Galantamine, Rivastigmine, Tacrine--increase cholinergic activity (activity that transmits nerve impulses within the parasympathetic nervous system)
- Management of neuropsychiatric symptoms is also important. Both drug and non-drug therapies are used. Medications utilised include:
 - · Antipsychotics - for agitation and psychosis
 - · Mood stabilisers - Carbamazepine, valproate
 - · Antidepressants - especially Selective Serotonin Reuptake Inhibitor
- Vitamin E - there is debate over its usefulness but may be prescribed by some physicians.

Non-Drug Therapy

is important and forms the backbone of day to day patient management and includes:

- · A calm environment, and a calm approach by caretakers
 - · Regular routine
 - · Ongoing mental stimulation
 - · Caretaker support
 - · Dementia specific nursing home care
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- The mainstay of treatment is supportive and each symptom is managed on an individual basis

Novel Diagnostics

- **Testing of at-risk asymptomatic adults** for EOFAD is clinically available for *PSEN1* (presenilin-1), *PSEN2* (presenilin-2), and *APP* mutations. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals
- **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 may have serious educational and career implications.
- **Prenatal diagnosis** for pregnancies at increased risk for a *PSEN1* mutation is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. Requests for prenatal testing is not common as of yet.

Novel Therapies of EOFAD Rising from Genetic Knowledge

- Beta-amyloid is the chief component of plaques, one hallmark Alzheimer brain abnormality. Scientists now have a detailed understanding of how this protein fragment is clipped from its parent compound amyloid precursor protein (APP) by two enzymes — beta-secretase and gamma-secretase. Researchers are developing medications aimed at virtually every point in amyloid processing. This includes blocking activity of both enzymes; preventing the beta-amyloid fragments from clumping into plaques; and even using antibodies against beta-amyloid to clear it from the brain.
- Preimplantation diagnosis and embryo transfer have been successfully used to achieve a pregnancy in a 30-year-old asymptomatic woman with an *APP* disease-causing mutation, resulting in the birth of a healthy child who does not have the *APP* disease-causing mutation identified in the mother and her family.

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Resources

- http://www.wrongdiagnosis.com/e/early_onset_alzheimers/treatments.htm?ktrack=kcplink
- <http://www.ncbi.nlm.nih.gov/books/NBK1236/#alzheimer-early.Diagnosis>
- <http://www.annualreviews.org/doi/full/10.1146/annurev.med.55.091902.103607>
- http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp