Early Onset Alzheimer's Disease and it’s Variants

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A little History

•Auguste Deter, the first person reported with AD neuropathology, appeared to have the onset of symptoms in her late 40’s, before being diagnosed with dementia at age 51.

• Her symptoms included memory loss, confusion, language impairment, and unpredictable, agitated, aggressive, and paranoid behavior.

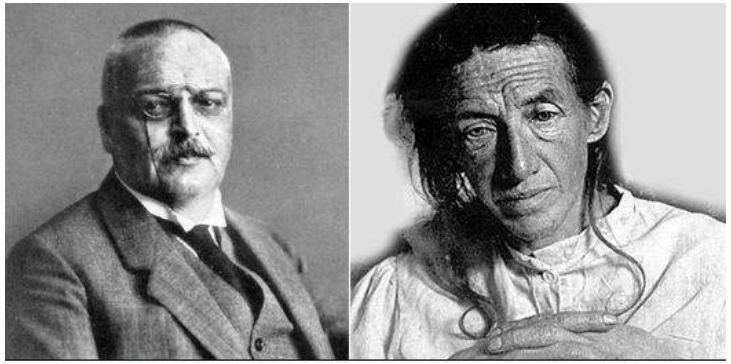
•At autopsy, Dr. Alois Alzheimer discovered that Ms. Deter had what we now recognize as the characteristic neuropathological markers of Alzheimer’s disease.

- Extracellular amyloid-positive plaques
- Intracellular tau-positive neurofibrillary tangles

• With the observation of similar neuropathology associated with cognitive decline in all age groups, investigators broadened the diagnosis of Alzheimer’s disease to include all age groups.

•The main focus of research in recent years has been on late-onset Alzheimer’s disease (LOAD).

•However, people like Ms. Deter – people with early-onset Alzheimer’s disease (EOAD) – remain an important and impactful subgroup of people with this disorder.



Alois Alzheimer Auguste Deter

INTRODUCTION TO EOAD

- Early-onset AD is defined as AD with clinical **onset younger than 65 years of age.**
- EOAD is the **most common cause** of early-onset neurodegenerative dementia.
- It comprises about 5% to 6% of all AD cases (roughly 200,000- 250,000 people).
- It is distinct from late-onset AD in a number of clinical, genetic, neurobiological, and management features
- EOAD accounts for at least one-third of patients with young-onset dementia, with the rest having vascular cognitive impairment, frontotemporal dementia, drug-related conditions, Lewy body disease, or autoimmune or infectious causes.
- The vast majority of individuals with EOAD have a sporadic, form of AD
- Approx. 11% with EOAD have familial AD assoc. With three of the known autosomal dominant mutations: **APP, PSEN1, or PSEN2.**
- Major difference is that approx. one-third (or more) with EOAD present with language, visuospatial, or other phenotypes rather than the usual amnestic disorder seen in LOAD

Criteria of AD

- Alzheimer's disease can be classified into 2 categories for practical purposes:
  - **Age of Onset**: Early v. Late
  - **Heritability**: Familial v. Sporadic

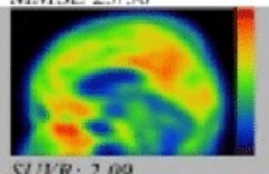
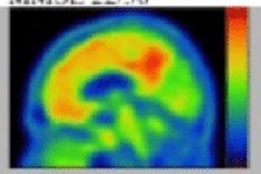
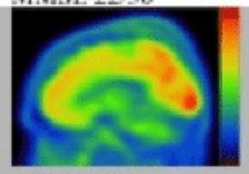
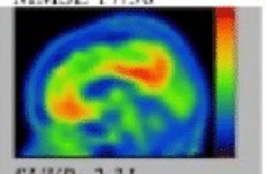
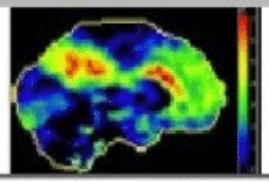
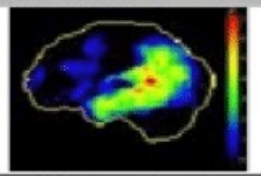
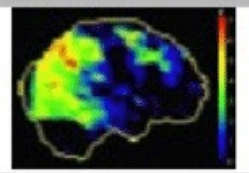
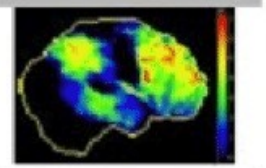
- Overall, AD is grouped into 4 categories:
  - Early-onset familial/Late-onset familial
  - Early-onset sporadic/Late-onset sporadic

- Sporadic v Familial EOAD
  - Sporadic EOAD: **lvPPA, PCA, and bdAD**
  - Familial EOAD: **PSEN1, PSEN2, APP, and APOE4**

Phenotypic Variants of Early-onset AD

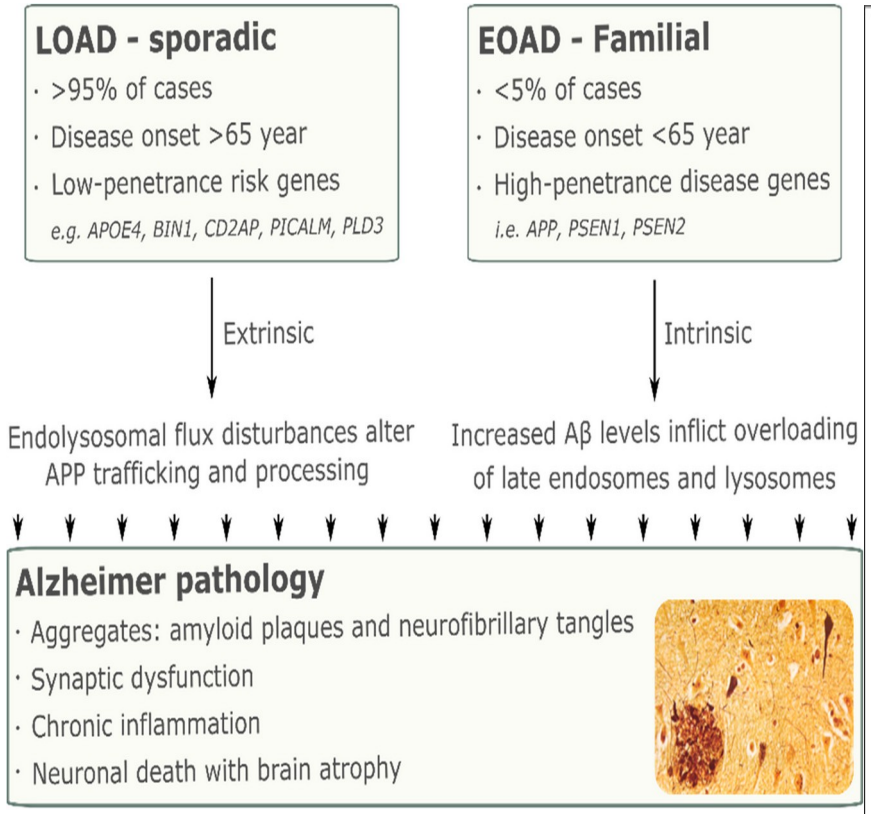
- Logopenic variant **primary progressive aphasia** [PPA])- Progressive decline in language with relatively spared memory and cognition.
- **Posterior cortical atrophy-** visuospatial or visuoperceptual impairment such as problems driving, getting dressed, and navigating surroundings.
- **Frontal or behavioral/executive** variants-prominent dysexecutive features accompanied by evidence of memory impairment.
- **Acalculia variant** with a parietal involvement.

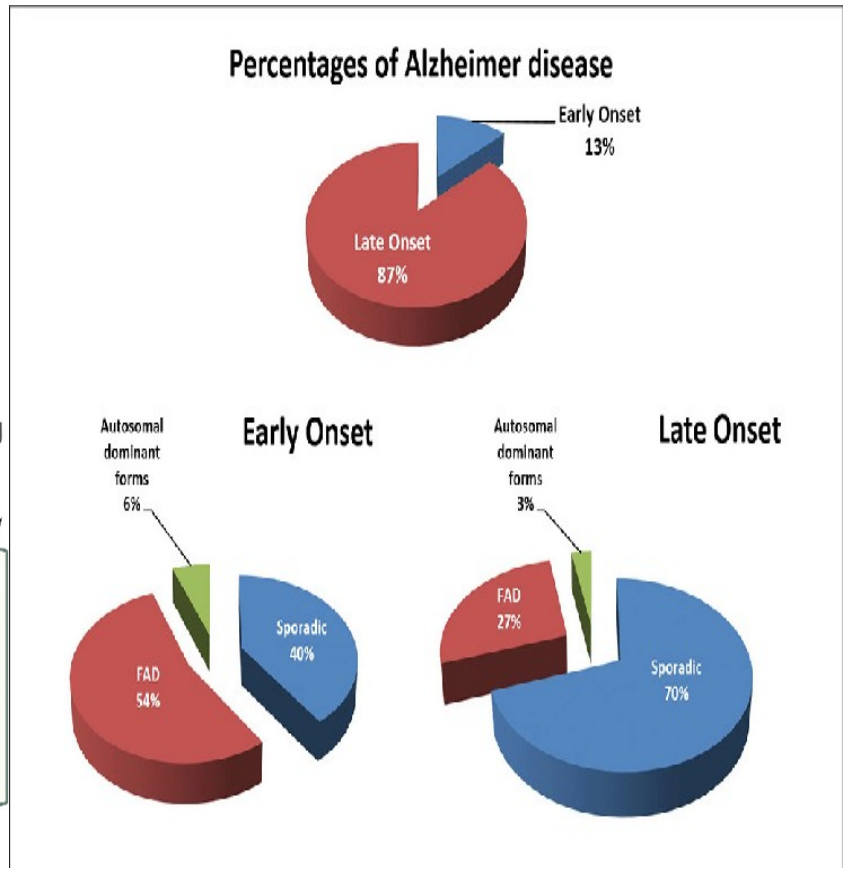
Comparison of Phenotypic variants of EOAD with Amnestic LOAD

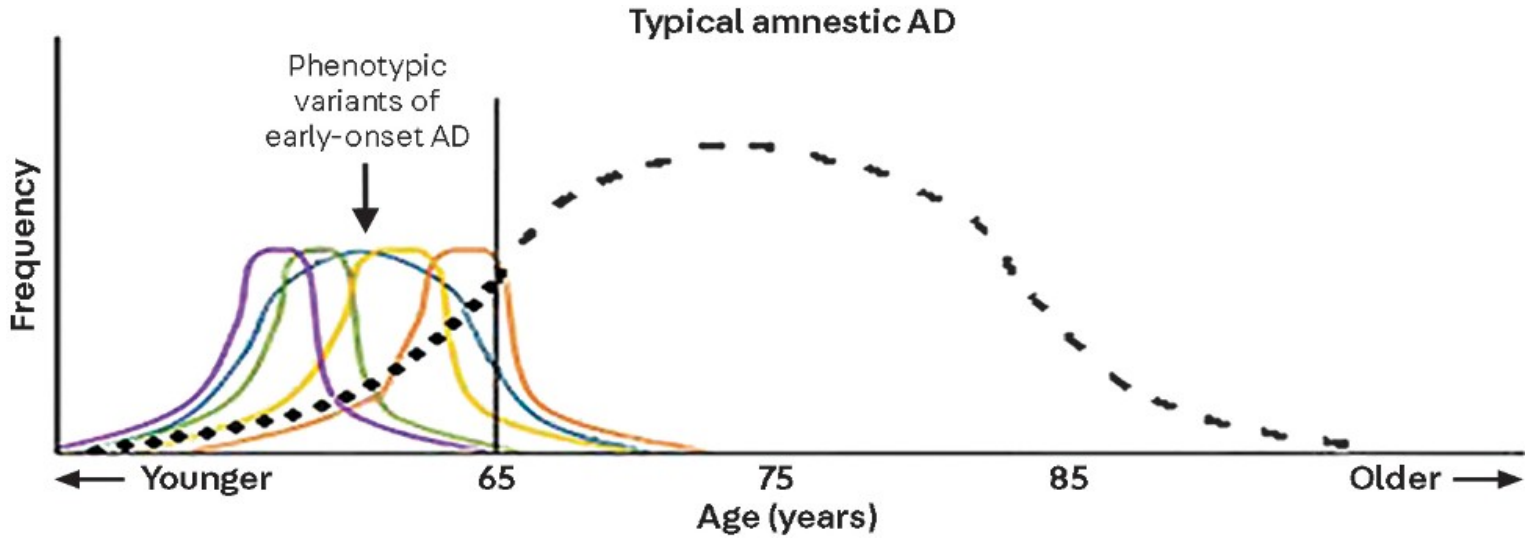
DOMAIN/ VARIANT	Amnestic	Language	Visuospatial	Behavioural-dysexecutive
Cognition	Memory loss Anomia Visuospatial deficits	Word-finding pauses Impaired repetition of sentences and phrases Phonological errors	Visuospatial defects Apraxia Simultagnosia Gerstmann's syndrome Alexia Prosopagnosia	Executive dysfunction
Behaviour	Mostly intact	Mostly intact	Mostly intact	Apathy Dishinibition Emotional blunting
Neurological	Head turning sign	Mostly intact	Visual field defects Optic ataxia Ocular apraxia	Mostly intact
Illustrative case	84 years old, F Insidious memory loss, apraxia, word-finding difficulties MMSE 23/30	68 years old, M Prominent word-finding difficulty, insidious memory loss MMSE 22/30	57 years old, F Visuospatial defects, marked apraxia, preserved memory MMSE 22/30	51 years old, F Marked executive deficits, dishinibition, behavioural changes MMSE 17/30
Amyloid imaging	 *SUVR: 2.09*	 *SUVR: 1.80*	 *SUVR: 1.98*	 *SUVR: 2.31*
FDG-PET				

MMSE: Mini-Mental State Exam; SUVR: Standardized Uptake Value Ratio (a positive amyloid study corresponds to a SUVR greater or equal to 1.5)

EOAD, Phenotypic variants vs LOAD cont.







Gene	Variant	Effect on EOAD	References
PSEN1	Promoter SNVs	Increased risk	[68], [69]
APOE	ε4 allele	Increase risk–highest in the presence of positive family history–and earlier AAO	[12], [70], [71]
	ε2 allele	Delays AAO	[70], [71], [72], [73]
CCL11	p.A23T	Delays AAO	[74]
PRNP	p.M129V	Increased risk–VV homozygosity and highest in presence of positive family history	[75]
	Octapeptide repeat insertions	Earlier AAO	[76]
SORL1	Nonsynonymous rare variants	Increased risk–signal driven by positive family history	[77]

Measure	ADAD findings	SAD findings
Clinical presentation	Episodic (recent) memory and judgment impairment in most; seizures and myoclonus not rare	Episodic (recent) memory and judgment impairment in most; seizures rare in early disease, more common in late disease
Atypical presentation	Yes – behavioral presentations; spastic paraparesis	Yes – behavioral and language presentations; posterior cortical atrophy
Age of onset	<60 years for most, can be as early as mid-20s; >60 years rarely reported	>60 years for most; <50 years rarely reported
Duration of illness	Average 6 to 9 years	Average 7 to 10 years
Atrophy – volumetric MRI	Hippocampal atrophy, temporo-parietal cortical loss	Hippocampal atrophy, temporo-parietal cortical loss
Hypometabolism – FDG-PET	Temporo-parietal hypometabolism	Temporo-parietal hypometabolism
Amyloid imaging – PiB-PET	Precuneus/posterior cingulate and prefrontal; consistent striatal binding	Precuneus/posterior cingulate and prefrontal; less consistent striatal binding
Pathology	Plaques and tangles in all; CAA in most; cottonwool plaques in some	Plaques and tangles in all; CAA in most
CSF Aβ42	Decreased	Decreased
CSF tau, p-tau181	Increased	Increased
Blood Aβ42/Aβ40 ratio	Increased	Variable

Key clinical features of Early-onset AD

- Large percentage of Non amnestic phenotypic variants (logopenic variant primary progressive aphasia, posterior cortical atrophy, behavioral/dysexecutive, acalculia, corticobasal syndrome)
- About 1 in 10 patients has an autosomal dominant familial Alzheimer disease (PSEN1, PSEN2, APP).
- Higher APOE ε4 frequency in amnestic early-onset Alzheimer disease but less in variant phenotypes .
- More aggressive course with high rate of mortality .
- Delay in diagnosis of about 1.6 years.
- Higher prevalence of traumatic brain injury (which lowers age of onset) and lower vascular risk factors

Key Clinical Features of Early-onset AD Cont.

- Overall less semantic memory impairment and greater attention, executive, praxis, and visuospatial difficulties.
- Hippocampal sparing and less mesial temporal lobe disease vs hippocampal and temporal lobe atrophy in LOAD.
- Higher burden of tau/neurofibrillary tangles per gray matter atrophy and stage of dementia, especially in focal phenotypic areas (reflected in tau imaging) .
- Greater posterior (parietal, temporoparietal junction) neocortical atrophy and hypometabolism vs temporal atrophy and hypometabolism.
- Amyloid PET is positive in most patients with early-onset AD who would not be expected to have age-associated brain amyloid deposition and can be useful in diagnosis of the disorder.

DIAGNOSIS of EOAD

Alzheimer's biomarker tests

TYPE OF TEST	STATUS
Blood tests	Recent progress on ultrasensitive tests for amyloid and tau in blood plasma could vastly expand testing for Alzheimer's disease by making it easier, safer and cheaper.
Cerebrospinal fluid tests	Abnormal amyloid levels in the cerebrospinal fluid are one of the earliest signs of Alzheimer's. Tau abnormalities tend to show up later, and may track better with cognitive decline.
PET brain scans	PET scans that use radioactive tracers to reveal amyloid accumulation in the brain (and newer scans that detect tau accumulation) are now widely used in Alzheimer's research, but not in clinical practice.
MRI brain scans	In later stages of the disease, evidence of neurodegeneration can be seen in MRI scans, which show brain anatomy in more detail than PET.
Genetic tests	The strongest genetic risk factor for late-onset Alzheimer's disease is a gene variant called *APOE ε4*. Researchers are working on tests that factor in smaller contributions made by many additional genes (see sidebar).

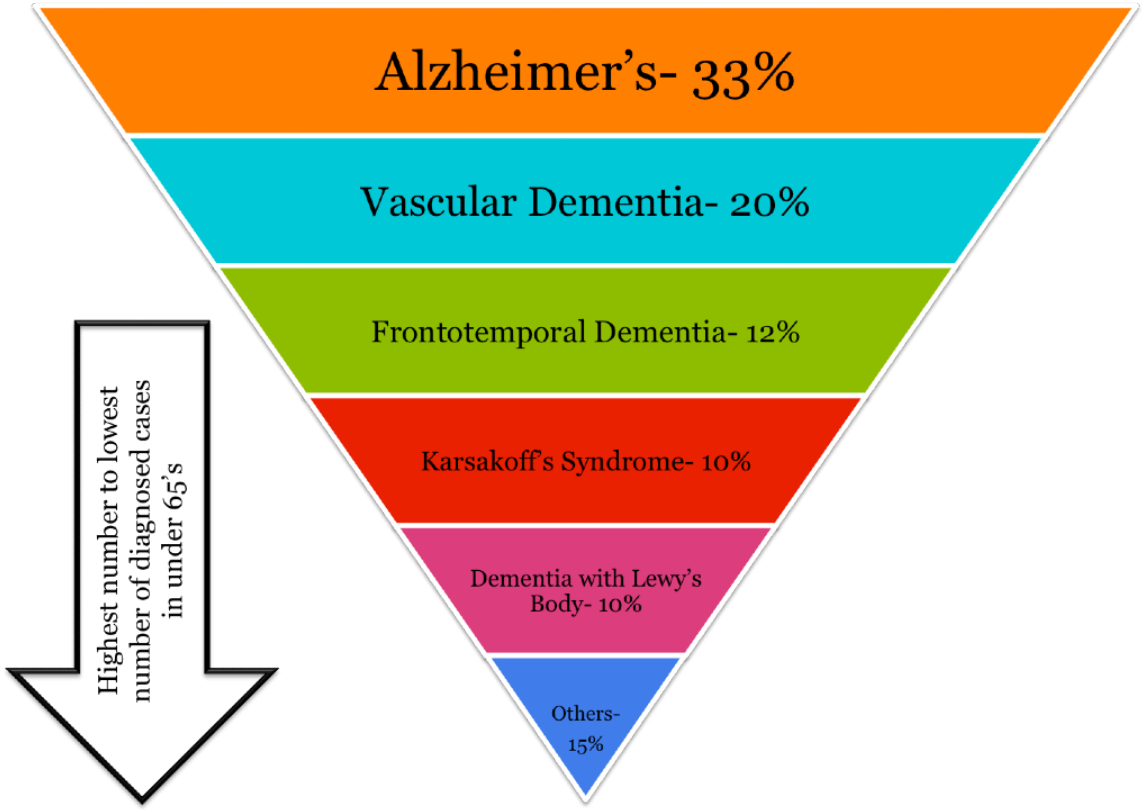
SOURCE: REPORTING BY G. MILLER

Differential diagnosis of EOAD.

Differential Diagnosis: Top Ten

(commonly used mnemonic device: AVDEMENTIA)

1. **A**lzheimer Disease (pure ~40%, + mixed~70%)
2. **V**ascular Disease, MID (5-20%)
3. **D**rugs, **D**epression, **D**elirium
4. **E**thanol (5-15%)
5. **M**edical / **M**etabolic Systems
6. **E**ndocrine (thyroid, diabetes), **E**ars, **E**yes, **E**nviron.
7. **N**eurologic (other primary degenerations, etc.)
8. **T**umor, **T**oxin, **T**rauma
9. **I**nfection, **I**diopathic, **I**mmunologic
10. **A**mnesia, **A**utoimmune, **A**pnea, **A**AMI
11. VA - consider PTSD, Gulf War Syndrome



Psychosocial and emotional considerations of EOAD.

- People with EOAD are often in the time of life when they are most productive and in the midst of careers and families.

- EOAD is more often associated with…
  - A sense of unexpected loss of independence in midlife
  - Anticipatory grief about the future
  - Difficulties with continued work, financial, and family responsibilities.
  - Individuals with EOAD and their families need specific education on this form of AD and what it means for someone who is middle-aged or relatively young.

- Compared to individuals with LOAD, individuals with EOAD often have the following;
  - Higher levels of disease awareness
  - Early generalized anxiety
  - Potential increased risk of suicide
  - Age appropriate support is needed but often difficult to find.

Management of Early-onset AD

- AchE inhibitors (donepezil, galantamine, and rivastigmine) with precautions and titration schedules.
- Speech therapy in patients with logopenic variant PPA.
- Patients with posterior cortical atrophy benefit from techniques and services for those who are partially sighted.
- Psychoactive medications to manage egregious behaviors in patients with behavioral/dysexecutive AD.
- Electronic calculation devices in those with acalculia may be beneficial.
- Occupational therapy in those with corticobasal syndrome.
- Genetic counseling for familial AD when the family history is suggestive of an autosomal dominant disorder.
- Provision of age-appropriate psychosocial support.

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THANK YOU!