An Examination of Early-Onset Alzheimer's Disease

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8TH ANNUAL KANSAS EDUCATION CONFERENCE ON DEMENTIA

NOVEMBER 14, 2019

Auguste Deter

A LITTLE HISTORY

- Alzheimer's disease originally meant a disorder of early-onset (<65 years of age)
- It did not include older individuals with "senile dementia"
- In fact, the first person reported with AD neuropathology, Austuste Deter, 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.

A LITTLE HISTORY cont.

- At autopsy, Dr. Alois Alzheimer discovered the 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.

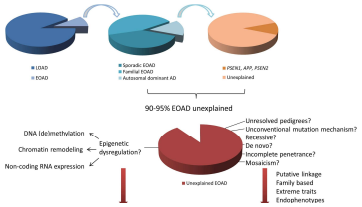
A LITTLE HISTORY cont.

- 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.

CURRENT STATUS OF RESEARCH

- Over the years, the primary focus on interest and research has been on late onset Alzheimer's disease (LOAD).
- The National Institute on Aging and the Alzheimer's Association have recently started the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) which is the first, large-scale study of EOAD
- Individuals with EOAD remain an important and impactful subgroup of individuals with this disorder.
- Unfortunately, not much is known about EOAD and its variants, hence the need for more research.

- *Cacace, R., Sleegers, K., Van Broeckhoven, C. (2016). Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimer's & Dementia: The Journal of the Alzheimer's Association,* 12, 733-748



EARLY-ONSET ALZHEIMER'S DISEASE

- EOAD is the most common early-onset neurodegenerative dementia
  - More common that ALS or Huntington's disease
- The age of onset demarcation line (65 years of age) is purely a sociological construct/partition based on age of retirement
- There is evidence to suggest that changing that demarcation age to 70 years of age would be more scientifically appropriate and effectively triple the number of EOAD individuals

EARLY ONSET ALZHEIMER'S DISEASE cont.

- EOAD 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
- Key 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
- The vast majority of individuals with EOAD have a non-familial, or sporadic, form of AD

EARLY-ONSET ALZHEIMER'S DISEASE cont.

- Only 11% or less of those with EOAD (about 0.6% of the total of all the individuals with AD of any age) have familial AD associated with one of the three known autosomal dominant mutations in APP, PSEN1, or PSEN2.
- An active area of research is the recognition of a polygenic risk for sporadic EOAD from a number of susceptibility genes.
- Management of EOAD my differ from LOAD when targeting specific cognitive and behavioral deficits.
- EOAD individuals must also consider genetic counseling.
- Age-appropriate psychosocial support is very important.

EARLY-ONSET ALZHEIMER'S DISEASE cont.

- For practical purposes, Alzheimer's disease gets defined on two criteria:
  - Age of Onset: Early v. Late
  - Heritability: Familial v. Sporadic
- This basically slices AD into four categories:
  - Early-onset familial/Late-onset familial
  - Early-onset sporadic/Late-onset sporadic

EARLY-ONSET ALZHEIMER'S DISEASE cont.

- Each subtype of AD is not a pure form unto itself.
- For example, a family is categorized as either EOAD or LOAD, but research shows that about 25% of families with LOAD also have relative who develops EOAD.
- In reality, AD exists in a continuum, a mix of gradations across these definitions.
- Focus of today's talk will be on sporadic and familial EOAD.
  - Sporadic: lvPPA, PCA, and bdAD
  - Familial: PSEN1, PSEN2, APP, and APOE4

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA

- Logopenic variant primary progressive aphasia (lvPPA) is the most common variant of EOAD
- Presents with progressive decline in language
- Relatively spared memory and cognition
- AD neuropathology in temporoparietal language areas in the left hemisphere

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA cont.

- Progressive aphasia has "logopenic" aspects, characterized by:
  - Difficulties in single-word retrieval
  - Repetition of sentences/phrase
  - Presence of phonologic errors,
- Temporoparietal degeneration disturbs the phonologic loop of working or echoic memory
- Results in impaired phonologic buffer for holding words or digits, hence the characteristic inability to repeat long sentences.

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA cont.

- History of dyslexia is common among patients with logopenic variant PPA
  - May indicate a preexisting vulnerability in language networks
- Other forms of PPA, such as nonfluent/agrammatic and semantic variants, are non-AD syndromes often due to frontotemporal lobar degeneration.

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA cont.

- An insidious onset and progressive disorder of language
- Word-finding difficulty with frequent word-finding pauses
- Overall decreased verbal output and slower rate
- Decreased word retrieval with phonologic paraphasia (errors)
- Disproportionately decreased repetition of sentences (hallmark finding)
- Decreased comprehension for long (not complex) sentences but not for words

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA cont.

- Preserved grammar (although it may be syntactically simple)
- Preserved motor articulation
- Other evidence of decreased phonologic store (e.g. – decreased digit or word span)
- Left posterior temporal/inferior parietal dysfunction on neuroimaging

POSTERIOR CORTICAL ATROPHY

- Posterior cortical atrophy (PCA) is the second most common early-onset AD variant
- Some studies have found that about 5 percent of people diagnosed with Alzheimer's disease have posterior cortical atrophy. However, because posterior cortical atrophy often goes unrecognized, the true percentage may be as high as 15 percent.
- Characterized by progressive and disproportionate loss of visuospatial or visuoperceptual functions.
- Usually due to Alzheimer degeneration of posterior cortical regions.

POSTERIOR CORTICAL ATROPHY cont.

- Core features of PCA
  - Insidious onset and gradual progression
  - Prominent visuoperceptual and visuospatial impairments but no significant impairment of vision itself
  - Relative preservation of memory and insight
  - Evidence of complex visual disorders (e.g., elements of Balint's syndrome or Gerstmann's syndrome, visual field defects, visual agnosia, environmental disorientation)
  - Absence of stroke or tumor

POSTERIOR CORTICAL ATROPHY cont.

- Individuals with PCA usually present with:
  - Visuospatial problems in reading
  - Problems manipulating or finding objects
  - Problems navigating their surroundings
  - Problems getting dressed
  - Problems driving

POSTERIOR CORTICAL ATROPHY cont.

- Early symptoms of PCA include:
  - blurred vision,
  - difficulties reading (particularly following the lines of text while reading) and writing with non-visual aspects of language preserved,
  - problems with depth perception,
  - increased sensitivity to bright light or shiny surfaces,
  - double vision and
  - difficulty seeing clearly in low light conditions.

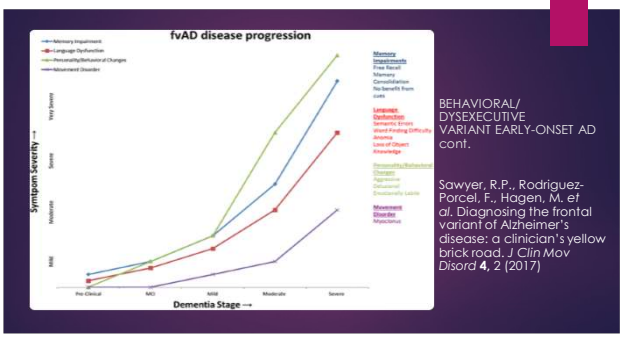
POSTERIOR CORTICAL ATROPHY cont.

- May have trouble accurately reaching out to pick up an object.
- As the disorder progresses, other symptoms evolve such as:
  - Getting lost while driving or walking in familiar places,
  - Misrecognition of familiar faces and objects
  - Will rarely have visual hallucinations.
  - Calculation skills and the ability to make coordinated movements are affected in some cases.

BEHAVIORAL/DYSEXECUTIVE VARIANT EARLY-ONSET ALZHEIMER'S DISEASE

- Previously called frontal variant Alzheimer's disease (fvAD)
- Not the same as behavioral variant frontotemporal dementia (bvFTD)
- bdAD and bvFTD can look alike and there is often a misdiagnosis (tendency to diagnose bvFTD over bdAD)
- People with bdAD are often distinguished from bvFTD because of the presence of prominent dysexecutive features accompanied by evidence of memory impairment

	CLINICAL FEATURES SUPPORTING BDAD	CLINICAL FEATURES SUPPORTING BVFTD
Memory	Early memory complaints	Late memory complaints
Language	Phonemic and semantic paraphasias	Loss of sociaemotional aspects of speech
Fluency	Semantic >phonemic fluency impairment	Phonemic >semantic fluency impairment
Behavioral	Compulsive or perseverative behaviors are uncommon	Collection or hoarding, and ritualistic and disinhibited behaviors (particularly involving food)
Personality Change	Agitation and irritability	Early apathy, disinhibition, loss of empathy
Thought Content	Delusions (theft, infidelity, and paranoid)	Mental rigidity
Body Habitus	Weight loss associated with depression	Weight gain associated with hyperphagia
Movement Disorder	Myoclonus (often mischaracterised as tremor), late parkinsonism	Early parkinsonism
Brain MRI pattern	Symmetric atrophy (temporal>frontal, posterior corpus callosum, and parietal/cun)	Symmetric (~MAPT mutations) or asymmetric (~GRN mutations) frontotemporal atrophy
CSF findings	CSF p-Tau/Aβ42 ratio (>0.21 ng/mL)	CSF progranulin levels (<60 ng/mL)- not validated in clinical practice
Biomarkers	APOE ε4 allele positive	No relation to APOE allele



BEHAVIORAL/ DYSEXECUTIVE VARIANT EARLY-ONSET AD cont.

Sawyer, R.P., Rodriguez-Porcel, F., Hagen, M. *et al.* Diagnosing the frontal variant of Alzheimer's disease: a clinician's yellow brick road. *J Clin Mov Disord* **4**, 2 (2017)

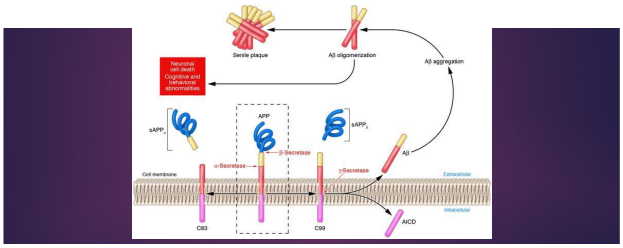
EARLY-ONSET FAMILIAL AD (eFAD)

- Autosomal-dominant forms of eFAD result from mutations on three genes.
  - Presenilin-1 (PSEN1) on chromosome 14
  - Presenilin-2 (PSEN2) on chromosome 1
  - Amyloid precursor protein (APP) on chromosome 21
- The APOE4 allele on chromosome 19 is also known to play a role as a risk factor, not as an autosomal dominant factor.

EARLY ONSET FAMILIAL AD cont.

- Evidence that PSEN1, PSEN2, and APP mutations cause eFAD by increasing the absolute or relative amount of Aβ42 derived from APP
- This over-production of Aβ has not been clearly demonstrated in sporadic EOAD, and the prevailing theory of the etiology of sporadic EOAD is that it results from decreased clearance of Aβ
- Familial AD can also have unusual pathological changes not seen in sporadic EOAD including increased deposition of Aβ in the cerebellum relative to sporadic EOAD
- Also clinical features such as gait abnormalities, early seizures, and myoclonus

Figure 2: The role of cerebral amyloid β accumulation in common forms of Alzheimer disease



J Clin Invest DOI: 10.1172/JCI25100

Measure	Autosomal Dominant AD findings	Sporadic AD 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 and tangles in all; Cerebral amyloid angiopathy in most
CSF Aβ42	Decreased	Decreased
CSF tau, p-tau181	Increased	Increased
Blood Aβ42/Aβ40 ratio	Increased	Variable

EARLY-ONSET FAMILIAL AD cont.

- Youngest age of onset seen with PSEN1.
  - Symptoms typically present between ages of 30 to 50 although younger has been observed.
- APP has slightly older age of onset
  - Symptoms typically presenting between ages of 45 to 60
- PSEN2 has wider range of onset
  - Symptoms typically appearing from 40 to even 80

EARLY-ONSET FAMILIAL AD cont.

- Majority of eFAD (autosomal dominant) have amnestic presentation similar to what is seen in LOAD
  - First deficits being in visual and verbal recall and recognition
- Neurological signs and symptoms appear to be more common in eFAD
  - Myoclonus and seizures are both relatively more frequent;
  - Myoclonus may be a harbinger of later seizures.
- A number of *PSEN1* mutations are variably associated with a spastic paraparesis (and characteristic histopathology) and extrapyramidal and cerebellar signs.

eFAD: Presenilin-1 (PSEN1)

- Identified in 1992 on chromosome 14, PSEN1 was the second gene discovered to have mutations found to cause inherited AD.
- Variations in this gene are the most common cause of familial AD
- Researchers know of 221 pathogenic mutations
- The family in Colombia has a PSEN1 mutation (E280A PSEN1)
- PSEN1 is considered to be a highly conserved membrane protein required for γ-secretase to produce β-amyloid

eFAD: Presenilin-2 (PSEN2)

- Discovered in 1993, PSEN2 mutations on chromosome 1 are found to cause familial AD
- Researchers know of 19 pathogenic mutations
- Presenilin is a subunit of γ-secretase. γ-Secretase participates in the cleavage of APP, which can produce different lengths of β-amyloid peptide (Aβ). The Aβ42 form aggregates easier than the Aβ40 form.
- PSEN2 mutation might increase γ-secretase activity.
- Some PSEN2 mutations cause an increased production of Aβ42, which is a major hallmark in the brains of patients with AD.

eFAD: Amyloid Precursor Protein (APP)

- Discovered in 1987, APP was the first gene with mutations found to cause an inheritable form of AD
- Researchers know of 32 pathogenic mutations
- Fully understanding the roll of APP has remained elusive
- Appears that APP has a role in synaptic formation and repair

eFAD: APP AND DOWN SYNDROME

- Down syndrome (DS) is associated with almost universal development of AD.
- Mean age of diagnosis is 55 y.o., with cumulative incidence of dementia being 95.7% by age 68.
- Increased risk driven by the overexpression of genes on chromosome 21, in particular APP
- Deposits of its protein product, β-amyloid, are a characteristic feature of AD and are found in the brains of adults with trisomy 21 by the mid-30s.

eFAD: APP AND DOWN SYNDROME cont.

- Neuropsychologically memory and attention start to decline in the 40s
  - Memory and attention scores sensitive to progression from preclinical to prodromal AD
  - Memory performance most sensitive to progression from prodromal to clinical AD
- AD in DS complicated by variable premorbid intellectual functioning and comorbid health issues including depression and hypothyroidism
- Possession of an APOE4 allele accounts for some variance

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 and information on this form of AD and what it means for someone who is middle-aged or relatively young.

PSYCHOSOCIAL AND EMOTIONAL CONSIDERATIONS OF EOAD cont.

- 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.

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