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Developments in understanding early onset Alzheimer's disease

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Abstract

On September 25 and 26, 2021, the Alzheimer's Association hosted the first meeting focused on people with early-onset Alzheimer's disease (EOAD)—sometimes referred to as younger onset Alzheimer's disease (AD). Though a diagnosis of AD can be devastating at any age, those with a younger onset—defined as symptoms developing prior to 65 years of age—face unique challenges. EOAD occurs when people are in the prime of their lives, often with multiple responsibilities including careers, community activities, and raising children and caring for older family members. These challenges warrant special consideration and study, yet people with EOAD are often excluded from AD research because of their atypical age of onset. To help fill this gap, we designed and launched the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) to enroll and follow 500 people with EOAD from > 15 sites in the United States, which the National Institute on Aging funded in 2018. The September 2021 meeting was designed to inform people with EOAD and their family members and caregivers about the latest research on the biology of EOAD, treatments in the pipeline, practical considerations about legal and financial arrangements for families, and the support networks available to them. More than 217 registrants attended.

Keywords

early-onset dementia; Longitudinal Early-Onset Alzheimer's Disease Study; natural history; neurodegenerative disease

1 | INTRODUCTION

As the population of the United States ages, the number of people developing Alzheimer's disease (AD) continues to grow. The vast majority of these develop cognitive impairment and dementia at age 65 or older, but ≈ 4% of those with AD develop their symptoms prior to age 65. This classifies them as having early-onset Alzheimer's disease (EOAD), which is estimated to include 200,000 to 300,000 people in the United States. An early age of onset does not equate to early stage of AD: people with EOAD can be at any stage of AD dementia, be it mild, moderate, or severe.[1,2]

There are unique challenges brought on by the development of dementia in middle age, when people commonly have additional familial, occupational, and community responsibilities beyond those for individuals diagnosed with late-onset AD (older than age 65). Families often endure a frustratingly protracted process before obtaining a diagnosis of EOAD, because medical professionals do not expect to diagnose dementia in adults in their 40s, 50s, or early 60s. The cognitive–behavioral symptoms of EOAD can derail employment for people when they are often at the height of their careers. This can lead to not only financial hardship, but also in some cases an identity crisis. Moreover, when an individual is diagnosed with EOAD, family roles are disrupted and major shifts are required in planning for the future.

Although people with EOAD share an early age of onset, their symptoms can differ, and dementia experts are working to define the different types.[1,2] The most common involves impaired memory and problem solving; this type resembles the more common late-onset

AD. In some cases the person's difficulties with problem solving (so-called "executive dysfunction") may be more prominent than memory loss (i.e., the dysexecutive variant of AD).[1] Less common are the posterior cortical atrophy type, which involves difficulty with integrating visual stimuli, and the logopenic primary progressive aphasia type, which affects language.[1] In both EOAD and late-onset AD, amyloid beta (Aβ) plaques and neurofibrillary tangles made of tau are present in the brains of people, with the specific patterns of accumulation and atrophy differing between these types with the former affecting the areas of the brain responsible for visual integration and the latter for language.[1]

Though genetic factors may drive early-onset disease, only 6% of individuals with EOAD carry known autosomal dominant mutations in the amyloid precursor protein (*APP*) or presenilin 1 and 2 (*PSEN1/2*) genes known to cause AD. This suggests that new genetic factors remain to be discovered, and this is supported by the family history of AD reported by half of EOAD cases. Genetic studies of people with EOAD promise to find new risk factors, as well as protective ones; both kinds of findings could offer therapeutic strategies to stave off the development of AD.[3] Notably, the apolipoprotein E (*APOE*) ε4 variant associated with risk in late-onset AD is less prevalent in EOAD.

Yet, individuals with EOAD are understudied, as their atypical young age often excludes them from large-scale studies. To fill this gap, the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) was established as a prospective, longitudinal multi-site observational clinical and biomarker study of EOAD.[4] Funded by the National Institute on Aging, LEADS seeks to define EOAD and its variants, to understand its progression, to find clinical outcome measures and surrogate biomarkers that can be of use in clinical trials for EOAD, to understand the impact of EOAD on people living with dementia and families, and to find resources to assist them.

2 | BRAIN AND BEHAVIORAL CHANGES RELATED TO COGNITIVE IMPAIRMENT

When a person in their early 60s or 50s (or younger) develops gradually progressive cognitive–behavioral symptoms, clinicians do not typically think of AD because it is uncommon at this age. In addition, people with EOAD sometimes present with symptoms that differ from the classic memory impairments associated with AD. Thus, recognizing the cognitive impairment, and discerning the cause—be it AD or some other neurodegenerative disease or other condition—is challenging but essential.

Different clinical syndromes within dementia affect memory, executive function, language, visual–spatial processing, and motor abilities. Characterizing the diverse set of changes in cognition and behavior is important because a diagnosis is useful clinically and can help identify therapeutic strategies, and because a diagnosis helps a person living with dementia and their family process the illness, plan for the future, and connect with research opportunities and support groups.[1]

To understand the cognitive function of a person with symptoms concerning for dementia, a clinician evaluates the individual's abilities in attention, executive function, learning

and memory, perceptual–motor abilities, language, and social cognition. To do so, it is critical for the medical professional to obtain a reliable history from the individual and from a family member or other close informant about the symptoms in daily life. In addition, the clinician will conduct cognitive testing with the patient. These evaluations try to capture any changes in a person's level of independent function, and may identify a recognizable cognitive–behavioral syndrome (such as progressive memory loss with executive dysfunction).[1]

Brain imaging and biomarkers can further pinpoint the causes of cognitive symptoms. Magnetic resonance imaging (MRI) can reveal changes in brain structure and identify specific brain regions undergoing atrophy. A glucose (fluorodeoxyglucose) positron emission tomography (PET) scan is often used to obtain a measure of brain function (metabolism), which is often abnormal in a person with EOAD. Aβ or tau PET scanning can identify regions with accumulation of AD-associated proteins. EOAD has its own pattern of brain atrophy that differs from typical late-onset AD: MRI scans of the brain in EOAD often do not show the hippocampal shrinkage typical of late-onset AD, but show rather dramatic shrinkage in the temporal and parietal cortex.[2] These findings match the non–memory-related cognitive impairments commonly found in EOAD involving executive function, language, and visuospatial processing.

2.1 | Transformative biomarkers

Biomarkers have transformed knowledge about AD. These measures provide a read-out of the hallmarks of AD, namely the Aβ plaques and neurofibrillary tangles composed of tau protein. PET scans or measures from cerebrospinal fluid (CSF) of these and other molecules can inform diagnoses, reveal the underlying disease processes, and shape clinical trials.

For diagnosis, current biomarkers obtained from CSF include Aβ and tau; in research we are also studying others like neurofilament light chain, neurogranin, and chitinase-3-like protein 1 (YKL-40). These measures reflect protein accumulation and neuronal/astrocytic dysfunction in the brain and have made it possible to confirm AD diagnosis without brain autopsy. PET scanning using radioisotopes that detect Aβ or tau has allowed direct observations of protein accumulation in the brains of living people.[5]

This capability is especially important for people with EOAD, for whom diagnosis is especially challenging. Approximately 75% of people enrolled in LEADS with early-onset cognitive impairment or dementia have evidence of elevated brain amyloid, which confirms the AD diagnosis; the remaining 25% are negative for amyloid.[4] The distribution of tau in the brain differs between EOAD and late-onset AD, however, and also varies between the different EOAD types.[1,4,6]

Biomarkers have also revealed the timing of brain pathology, which can precede cognitive impairment by decades. Aβ and tau initially accumulate in the brain, followed by a period during which Aβ reaches a plateau while tau continues to accumulate, and then spreads throughout the brain. This spread is associated with cognitive changes and memory loss. Though the precise patterns of accumulation differ among subtypes of dementia, this general timeline suggests that finding ways to lower Aβ early on could prevent tau spread, and the

associated cognitive decline; it also suggests that treatments to reduce tau are important as well. [5,7]

Recently biomarkers have been used to select participants and to titrate drug dosage in multiple clinical trials of anti-amyloid medications.[8,9] PET scans with Aβ tracers identified people whose brains were Aβ positive, and thus eligible to participate. Scans conducted throughout treatment demonstrated decreases in Aβ, evidence that the medication is accomplishing its goal. More importantly, several of these studies also demonstrated a slowing of cognitive decline. At the time of the conference, participants were awaiting the results of phase 3 trials of medications aiming to slow disease progression.

Blood tests for brain Aβ, tau, and other molecules are under development. Recent work finds that blood levels of Aβ fragments accurately identify amyloid status in the brain 88% of the time, and blood levels of phosphorylated tau identify tau brain status 96% of the time.[9] Once sufficiently accurate, these kinds of blood tests will provide less costly and more accessible measures than current biomarkers.

2.2 | Amyloid-modifying drug therapies

In June 2021, the US Food and Drug Administration (FDA) approved a new AD drug called aducanumab under its accelerated approval pathway, which proved to be a controversial decision that has riven the field. Aducanumab (Aduhelm) is a monoclonal antibody designed to target and remove Aβ from the brains of people with AD, which it does effectively. The controversy turns largely on the clinical benefits, as the evidence is ambiguous about whether this robust lowering of brain Aβ affects cognition.

A panel discussed aducanumab and other amyloid-targeting drugs in the pipeline, and whether EOAD individuals might be candidates for clinical trials of these types of drugs. The panel expressed excitement about aducanumab and similar treatments, which represent a new drug class that acts on and removes a key pathology thought to drive AD.

The aducanumab accelerated approval raises questions about what can be expected clinically. To receive full approval, the FDA has traditionally wanted to see clinically meaningful effects, which means improvements in memory and everyday functions that are noticeable to the persons living with dementia or their family. Yet the ambiguous cognitive benefits so far suggest that intervening earlier, before brain pathology is too far along, may be the best strategy.

The decades-long disease process of AD makes it challenging to identify the optimal window for treatment. It may be appropriate to treat people in the early stages of disease, namely mild cognitive impairment (MCI) due to AD, and who also have Aβ buildup in the brain. Those with EOAD may also be eligible: the aducanumab clinical trial participants were aged between 50 and 85 years old, so the drug reduced amyloid in some younger onset individuals.[10] Treating younger individuals, including those with EOAD, may also slow down cognitive decline, complicating co-morbid pathologies in the brain such as vascular damage, Lewy bodies, or TAR DNA-binding protein 43 accumulation associated with frontotemporal dementia.

Treating even earlier, before cognitive changes develop, might also be an effective strategy. Those carrying rare autosomal mutations in *APP* and *PSEN1/2*, who are likely to develop AD in middle age, are candidates for this very early stage strategy. A trial of a different amyloid-targeting antibody called gantenerumab in this group by the Dominantly Inherited Alzheimer Network (DIAN) had similar results to aducanumab, with a successful decrease in Aβ in the brain, but no clinical benefit.[11] This trial included people who didn't yet have clinical signs of dementia, and who are now continuing treatment. The trial extension will test the idea that keeping Aβ low in this group can have a long-term benefit for cognition. Another trial called the Primary Prevention Trial will test whether treatment with gantenerumab even earlier, before Aβ accumulates in the brains of people carrying dominantly inherited mutations, will benefit them.

These therapies come with risk of amyloid-related imaging abnormalities (ARIA), which reflect cerebral edema or hemorrhages in the brain. These come about as the Aβ antibodies remove Aβ from the brain into the bloodstream, which causes leaks in the blood–brain barrier. Those who carry the *APOE* ε4 allele are at a greater risk of these side effects.[10] Often ARIA is asymptomatic or mild, and can resolve on its own, but in rare cases it could result in significant impairments.[12] ARIA is an important consideration when weighing risks and benefits of antibody treatments.[10]

Ultimately, the controversy surrounding aducanumab's approval pushes the field to improve the precision of the trials, and may prompt regulatory agencies to refine their procedures to better deal with diseases that unfold over decades. Resolving these questions sharpens the science, and combined with biomarker developments, will facilitate research into AD treatment. One of the benefits of participating in LEADS is that people are able to obtain a confident diagnosis about whether their symptoms are likely due to AD or not, which is the key to determining whether they would be candidates for these drugs once they are FDA approved. We hope through LEADS to facilitate access to currently approved as well as experimental treatments.

2.3 | Personal perspective on the importance of early diagnosis

The authors of *Finding the Right Words* offered a personal perspective on the importance of receiving an early diagnosis. Cindy Weinstein shares this story in her memoir *Finding the Right Words*, co-authored with neurologist Bruce Miller at the University of California San Francisco (https://weinsteinandmiller.com/finding-the-rightwords). She recounted how her father was diagnosed with EOAD in 1985 when he was 58 years old, how the family was left on their own to deal with it, and how learning more about the science of dementia since then has helped her process his illness.

As part of this, she learned that her father had the logopenic variant of EOAD, which helped explain his word-finding difficulties. She also noted that some of his early symptoms such as sleep and hearing difficulties, and depression symptoms, were likely early signs of his illness. Weinstein also emphasized the need for empathy among neurologists and health-care workers. Though things have improved since the 1980s, she says that even a simple "How are you doing?" or "Whatever question you have, please ask," can be very reassuring and comforting for people living with dementia and their families.

2.4 | Resources to support people living with dementia and their families

A diagnosis of EOAD forces the individual and their family to face important financial, legal, and medical challenges. An elder law attorney described her experiences helping young families navigate the issues necessitated by an EOAD diagnosis. She recommended that a person living with dementia and their family meet with an attorney specializing in elder law soon after the diagnosis, which would allow them to put plans in place when the person with EOAD can still express their goals and preferences.

To find a suitable attorney, families may consult the National Academy of Elder Law Attorneys (NAELA; https://www.naela.org). This consists of a group in the United States who specialize in elder care and disability care law, which may be a good fit for EOAD families. Families will want someone who can take care of documents like health-care proxies or durable powers of attorney to authorize certain people to make decisions on behalf of a person with EOAD; they will also want an attorney who has experience helping families access resources for benefits or to pay for care. The cost of an attorney varies, but a reputable one will be up front about their price. An hour of advice from an attorney early on may make economic sense if it allows the family to make decisions with good information instead of in fear.

Representatives from the Alzheimer's Association described the support groups and resources developed by the Alzheimer's Association to help people living with dementia, their families, and caregivers. After a diagnosis, these supports can help people with AD figure out how to live well despite the diagnosis, connect with others, develop strategies to manage cognitive impairments, and bolster social engagement. For caregivers these resources can help educate them about the disease, let them know what to expect, offer different caregiving strategies, plan for the future, and connect with others.

Specifically, the Alzheimer's Association has established a 24-hour help line (800-272-3900) staffed by master's level care consultants who can give personalized help, disease information, problem solving, and ideas for caregiving strategies. The Alzheimer's Association has also organized support groups in communities for those with AD and for their caregivers (alz.org/crf). Education programs went virtual in the pandemic, and some of these are specific for EOAD (alz.org).

Online resources are also available on the Alzheimer's Association website for people with AD and for their caregivers. This includes a special section on EOAD. These resources include information about every stage of AD, medical care, safety issues, and legal and financial planning (alz.org/elearning). The Alzheimer's Association has also established an online message board called ALZConnected. This is an online community with different forums for people with AD and for their caregivers, including one for EOAD (alzconnected.org).

The Alzheimer's Association has also developed a powerful advocacy program in which volunteers across the United States advance AD priorities in federal and state governments. The consistent and vigorous efforts of these advocates to reach state and federal representatives have wrought huge changes in AD research funding: in 10 years funding

by the federal government for AD research has increased 7-fold, now amounting to $3.2 billion per year. This kind of investment promises to change the nature of the disease, and advocates attest to this work as one of the most powerful ways to make a difference for the future.

3 | CONCLUSION

People with EOAD face cognitive difficulties while in the prime of their lives. Highlighting the unique challenges faced by this understudied population, the LEADS family meeting held in September 2021 gathered > 200 registrants to hear scientific and pragmatic sessions focused on EOAD. The scientific presentations gave background on this disease; updates on the search for EOAD-related biomarkers and their potential use in clinical trials of potential treatments; and reports on LEADS, the first study designed specifically to study EOAD. Practical discussions focused on legal and financial concerns of those diagnosed with EOAD and their families, and highlighted available resources for support for patient and caregivers alike. Together the discussions validated the need for increased attention, research, and resources to people with EOAD and their families.

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RESEARCH IN CONTEXT

1. **Systematic Review**: The Longitudinal Early Onset Alzheimer's Disease Study is the largest study of its kind focused on younger onset dementia due to Alzheimer's disease and dementia due to unknown causes. Previous work has identified familial mutations associated with younger onset Alzheimer's disease. The work in this study will help us understand natural history, progression, pathology and genetics associated with sporadic younger onset dementia.
2. **Interpretation**: The family meeting provides valuable education and support sessions for people living with younger onset dementia. This meeting is designed in collaboration with people living with younger onset dementia, their family members and caregivers to ensure that the scientific content resonates with the participants.
3. **Future Directions**: Future meetings will continue to engage those living with younger onset dementia due to Alzheimer's disease and dementia due to unknown causes to ensure the content deliver remains relevant to them.