Update on the Science of Alzheimer’s Disease and Dementia
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Conflicts of Interest

The presenter has no conflicts or professional relationships to disclose relative to this content
What is Dementia? 
AD the Most Common Form

![Pie chart showing the distribution of different types of dementia]

Topics
- Epidemiology
- Effects of Dementia on the Brain
- Causes and Risk Factors
- Diagnosis
- Available Therapies and Treatments
- The National Plan to Address AD
- Clinical Trials/ New Risk Genes
AD and Overall Dementia Epidemiology

- Rates increase exponentially from 60-90 years of age
  - The lifetime risk of Alzheimer's in the general population is 10-15%.
  - Having a first degree relative with Alzheimer's approximately doubles the lifetime risk to 20-30%
- Steady increase with age until mid-80's: approx. 40-50% affected
- US: approximately 5 million currently (8-10 million with dementias)
- Expected to increase to 12-15 million by 2040
- 24 million worldwide with dementia; 4.6 million new cases yearly
- Dementias substantially reduce life expectancy
  (67% reduction at age 65; 39% reduction at 90 years)
- Nursing home admission ~75% of AD patients by 80yo vs. 4% of the general population

Alois Alzheimer

Alzheimer observed Auguste Deter at the Frankfurt Asylum in 1901. The 51-year old patient suffered behavioral symptoms of progressive short-term memory loss of unclear cause.

Mrs. Deter expired in 1906. Alzheimer had the patient records and brain brought to Munich where he was working in Emil Kraepelin's lab. He used tissue staining techniques to identify amyloid plaques and neurofibrillary tangles.

On November 3, 1906 he presented report of the pathology and clinical symptoms of presenile dementia. Kraepelin described “Alzheimer's disease” in an influential 1910 textbook. By 1911, his description of the disease was being used by European trained physicians to diagnose U.S. patients.
**Characteristics of Alzheimer’s Disease**

- Slow, insidious onset of cognitive changes
- Gradual worsening of symptoms
- Short-term memory and cognitive complaints usually predominate
- Social and emotional behavioral (“personality”) changes common
- Progression to impaired activities of daily living (e.g., shopping, driving, finances, cooking etc.)

**Other Patterns of Dementia**

- **Parkinson’s disease** dementia: 5-10 years after motor symptom onset
- **Lewy Body**: parkinsonian symptoms along with behavioral changes
- **Vascular**: irregular onset; vascular risks factors and stroke events predominate
- **Frontotemporal**: language, spatial, social variants; memory not leading symptom
- **Normal Pressure Hydrocephalus**: Triad of gait, incontinence, mental slowing
- Medications, Trauma, Cardiac, Sleep Apnea etc.
Effects on the Brain


Cellular/Molecular Bases of AD

Inflammation
Mitochondrial dysfunction
Oxidative stress
Tau proteinopathy
Apoptosis

Amyloid beta oligomers
Amyloid beta plaques

Mucke, 2009
Limbic Age TDP-43 Encephalopathy

Disease Characteristics

- Perhaps a **decade time lag** between start of pathology and symptoms

- **Stages:** Preclinical, Mild Cognitive Impairment (MCI), Early Dementia, Moderate Dementia, Severe Dementia

- Numerous associated **risk factors:**
  - Aging, Hypertension, Cholesterol, Vascular, TBI
  - Obesity, Diabetes, Glucose intolerance, Sleep apnea
  - Depression, Hearing loss, Social Isolation, Genes

- **Protective:** cognitive-social-physical activities, Mediterranean style diet, metabolic health, mental health
Diagnostic Workup

Medical/Neurologic Hx
- Both the patient and a reliable informant

Office-based clinical assessment
- Comprehensive physical examination
- Neurologic and mental status evaluation
- Review of medications

Lab Tests
- Comprehensive blood chemistries (e.g., CBC, RPR, liver function, thyroid, vitamin B12 etc.)
- Brain imaging- MRI/CT

Neurocognitive testing
- Memory
- Executive functions
- Spatial, Attention, Language
- Emotional

Progression of Disease

- Recent Memory Loss
- Confusion Episodes
- Difficulty Performing Familiar Tasks
- Word Finding Struggles
- Disorientation to Time & Place
- Altered Executive Functions and Judgment
- Problems With Abstract Thinking
- Misplacing Items
- Changes In Mood & Behavior
- Changes In Personality
- Loss of Interest in usual Activities
- Social Withdrawal
Amnestic Mild Cognitive Impairment (MCI)

- Memory complaints, confirmed by informant
- Measureable memory impairment by cognitive testing
- Other cognitive functions preserved
- ADL’s not impaired, maintains most usual activities
- No dementia symptoms, no confusional episodes

“High Risk Group”
Approx. 20% of persons 65+
Risk for AD 15-20% conversion rate per year
Some will remain with MCI symptoms and not progress

Treatment Approach

- Correct any treatable blood chemistry, medication side effect or brain imaging conditions
- Correct sleep, nutritional, metabolic health and psychosocial factors
- Consider FDA approved medications (donepezil/Exelon and memantine) to stabilize cognitive decline
- Continue follow-up care for driving, living, caregiving, NIH recommendations and medical care
Benefits of Acetylcholine-related Med
(donepezil/Aricept, Exelon patch)

- Cognition:
  - Many trials have shown statistically significant improvement over placebo on measures of cognition and measures of overall improvement.

- Secondary endpoints have shown:
  - Improved ADL’s in mild to moderate AD, unclear in severe AD
  - Fewer neuropsychiatric symptoms in mild to moderate AD (but not agitation)
  - Delayed placement to nursing homes
  - Less burden to caregivers

Memantine

- NMDA receptor antagonist
- Indication: Moderate-severe AD
- Dosing: Twice a day
- Evidence of efficacy with or without donepezil:
  - Improvement on measures of cognition, clinician global impression and ADL’s
  - Improvement on measure of neuropsychiatric symptoms

Reisberg, et. al. NEJM. 2003
Tariot, et. al. JAMA. 2004
Finnish Geriatric Intervention Study

2-year multicenter randomized trial with 1260 participants (60-77 yo). Participants randomized into a multidomain intervention group or control group. Multi-domain intervention components were:

- Dietary guidance
- Physical activity
- Cognitive training and social activities
- Intensive monitoring and management of metabolic and vascular risk factors
- Controls received regular health advice.
Finnish Geriatric Intervention Study

- Changing these lifestyle factors reduced the risk of cognitive decline by 30%
- Extended follow-up studies are underway
- NIH Recommendations:
  - Meet metabolic health targets
  - Exercise at least 3x/week (30 minutes), daily better
  - Mediterranean style diet
  - Consistent and sufficient sleep (address any disturbances)
  - Daily social, recreational and cognitive activities

National Plan to Address Alzheimer’s Disease

- Create and maintain an integrated national plan to overcome AD.
- Coordinate AD research and services across all federal agencies.
- Accelerate the development of treatments that will prevent, halt, or reverse AD
- Improve early diagnosis and coordination of care and treatment of AD.
- Improve outcomes for ethnic and racial minority populations that are at higher risk for AD.
- Coordinate with international bodies to fight AD.
Pennsylvania Alzheimer’s Initiative

- An estimated 280,000 Commonwealth residents are living with Alzheimer’s disease; 400,000 when considering related dementias
- Governor Corbett created the Pennsylvania Alzheimer’s Disease Planning Committee (2013)

Pennsylvania Alzheimer State Plan Task Force

- Working with local organizations, entities, advocates, and other stakeholders to identify and share best practices. Review and revise the state plan.
- Develop and facilitate actions to carry out the plan
- Pursue research and review issues that relevant to AD and related disorders
- Assist in planning annual Alzheimer’s Disease and Related Disorders Forum
- Assist in development of annual plan update
- Recommended response strategies to the rising number of those affected by these diseases
Clinical Trials

- More than 80 ongoing
- Intranasal insulin: upregulating
- Coconut oil supplement
- Resveratrol: anti-oxidant
- Statin: clearing cholesterol
- Amyloid clearing drugs
- Neuroprotectives & neurotrophics

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MIND Study now available (www.MINDstudy.org)
Nicotine patch vs. placebo over 2 year trial
Nicotine acts similarly to acetylcholine (important neurotransmitter for memory and cognition)
6 month trial has already shown beneficial results
Enrollment in our clinic
PET Imaging in AD-Clues to Treatment

Red areas indicate amyloid accumulation

Blue-green areas indicate hypometabolism of brain cells

The Alzheimer's Prevention Initiative APOE4 Tria;

- 5 - year prevention trial
- Tests an **anti-amyloid drug** in cognitively normal older volunteers who are at increased risk of developing late-onset Alzheimer’s because they inherited two copies of the ApoE4 allele, the best known genetic risk for late-onset disease.
- The study tested the role of amyloid in the development of AD
- Anti-amyloid drugs have not been successful in treatment trials to date
Allopregnanolone Regenerative Therapeutic for MCI/Alzheimer's: Dose Finding Phase 1

- This is an early-phase clinical trial to evaluate over 12 weeks the safety and tolerability of increasing doses of allopregnanolone, a natural brain steroid, in treating mild cognitive impairment and Alzheimer's disease.
- The drug has been shown to promote the generation of new brain cells, reduce amyloid levels, and restore cognitive function in pre-clinical animal testing.

Stimulating the Innate Immune System to Prevent Alzheimer's

- This 24-week, randomized, double-blinded, placebo-controlled study will recruit patients with mild cognitive impairment.
- This is a three-year, Phase II proof-of-concept study.
- Seeks to evaluate potential use of recombinant sargramostim, a drug that stimulates the innate immune system, to determine whether it may clear abnormal amyloid deposits before they cause damage.
- As a result of this clearance, it may either prevent cognitive decline or possibly arrest or improve cognition.
AD Awards

- Pathway Discovery, Validation and Compound Identification for Alzheimer's Disease – a systems biology approach to complex molecular networks and candidate genes
- Integrative Biology Approach to Complexity of Alzheimer's Disease - apply innovative analytical methods to large-scale molecular, cellular and clinical data from AD patients to construct biological network models
- A Systems Approach to Targeting Innate Immunity in Alzheimer's - to identify and characterize novel therapeutic targets within the innate immune system

New Risk Gene Discoveries

- The search for late-onset Alzheimer’s risk factor genes has taken considerable time. Until 2009, only one gene variant, Apolipoprotein E-e4 (APOE-e4), had been identified as a known risk factor.
- Since then the list of known gene risk factors has grown to include other players—PICALM, CLU, CR1, BIN1, MS4A, CD2AP, EPHA1, ABCA7, SORL1 and TREM2. – implicated in immune system, cholesterol metabolism, and synaptic dysfunction and cell membrane integrity
Prediction of Disease Progression

- A polygenic hazard scoring (PHS) method is developing
- 21 single nucleotide polymorphisms (SNPs) with strongest ties to AD
- The higher the PHS, the more amyloid load and tau tangles

Young Onset AD Genetic Patterns

- About 60% is familial
- About 13% have a family member in almost every generation with the disease.
- This type of inheritance is called **autosomal dominant**. In these cases only one copy of the gene from either parent is required for a person to be affected.
Young Onset AD Genes

- Mutations in **three genes** known to cause early onset AD. All involve increased beta-amyloid.
- Of those with autosomal dominant early onset AD, 30-70% of families carry a mistake in the gene **presenilin-1** on chromosome 14.
- About 5-15% have a genetic fault on chromosome 21 in the **amyloid precursor protein** gene.
- A very small group of families has a fault on chromosome 1 in the **presenilin-2** gene.
- Having one or two copies of the **apoE-ε4** gene does not cause young onset AD.

The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Trial

- Testing new **anti-amyloid-beta drug** treatments in volunteers who have an inherited form of AD.
- Amyloid plaques are a hallmark of AD. Anti-amyloid-beta therapies attempt to treat plaques.
- 4-year trial, multi-site international effort. Three anti-amyloid-beta interventions.
- Now being expanded
I strongly endorse memory and cognitive screening for all older persons by their primary care provider - public health perspective.

- Incidence of dementia rises with each decade after 50.
- There is a great deal of variability in memory functions, health and aging - individual patient perspective.
- Individual screening for baseline with primary care provider and follow-up assessments as needed.
Brain Health Interventions

- **Lifestyle factors:**
  - Sleep
  - Nutrition
  - Exercise
  - Cognitive-Social-Recreational Activities
  - Look at ways to bring feasible technology into play in everyday activities
  - Medications and metabolic health

Summary

- Clearer commitment to find a cure
- Greater coordination of clinical and research resources
- Better caregiver resources and support systems
- Increased attention to early detection and routine screening as part of regular healthcare
- Multiple clinical trials ongoing
- Innovative genomic analyses emerging
- Focus on lifelong lifestyle factors