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SPECTRUM HEALTH

MICHIGAN STATE UNIVERSITY
College of Human Medicine

Welcome to the *Your Health Lecture Series!*

Tonight's Lecture:
Early Alzheimer's Disease:
Decision Making & Promising Research

Lecture Begins @ 7:00pm
Tonight's event is being livestreamed to Spectrum Health!
Refreshments available in room 123

Dr. Timothy Thoits

Neurologist
Spectrum Health Medical Group

Clinical Associate Professor
Michigan State University College of Human Medicine

Tonight's focus area:

Research regarding early diagnosis and prevention

Dr. Cindy Beel-Bates

Professor of Nursing
Grand Valley State University

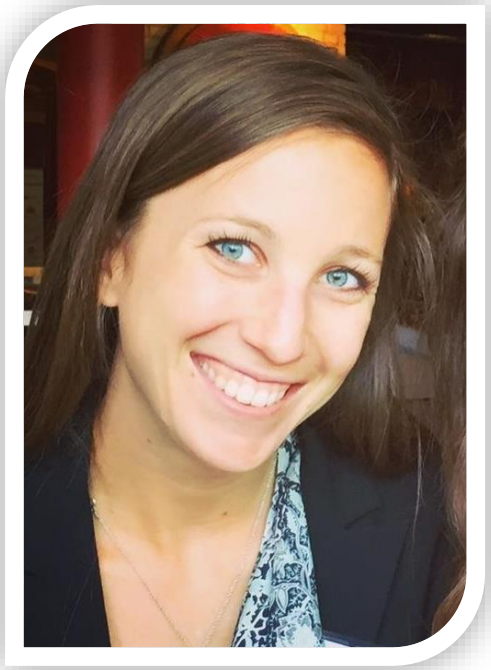
Tonight's focus area:

Non-drug intervention for quality of life

Lisa Ellens

Director

Rethinking Dementia Accelerating Change



Tonight's focus area:

Decision making and local resources

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Alzheimer's disease: Before The Fall

November 12, 2015

Disclosures

No disclosures

Goals

Diagnosis of Alzheimer's disease

Alzheimer's disease

- pathology
- asymptomatic stage
- premorbid stage

Definition Alzheimer's disease

NINCDS-ADRDA

Gradual and progressive loss of memory over 6 months

Objective evidence of impaired memory on testing when cueing does not help

Plus one or more supportive features:

temporal lobe atrophy

low CSF $A\beta_{42}$

increased CSF t-tau

increased CSF phosphorylated tau (p-tau)

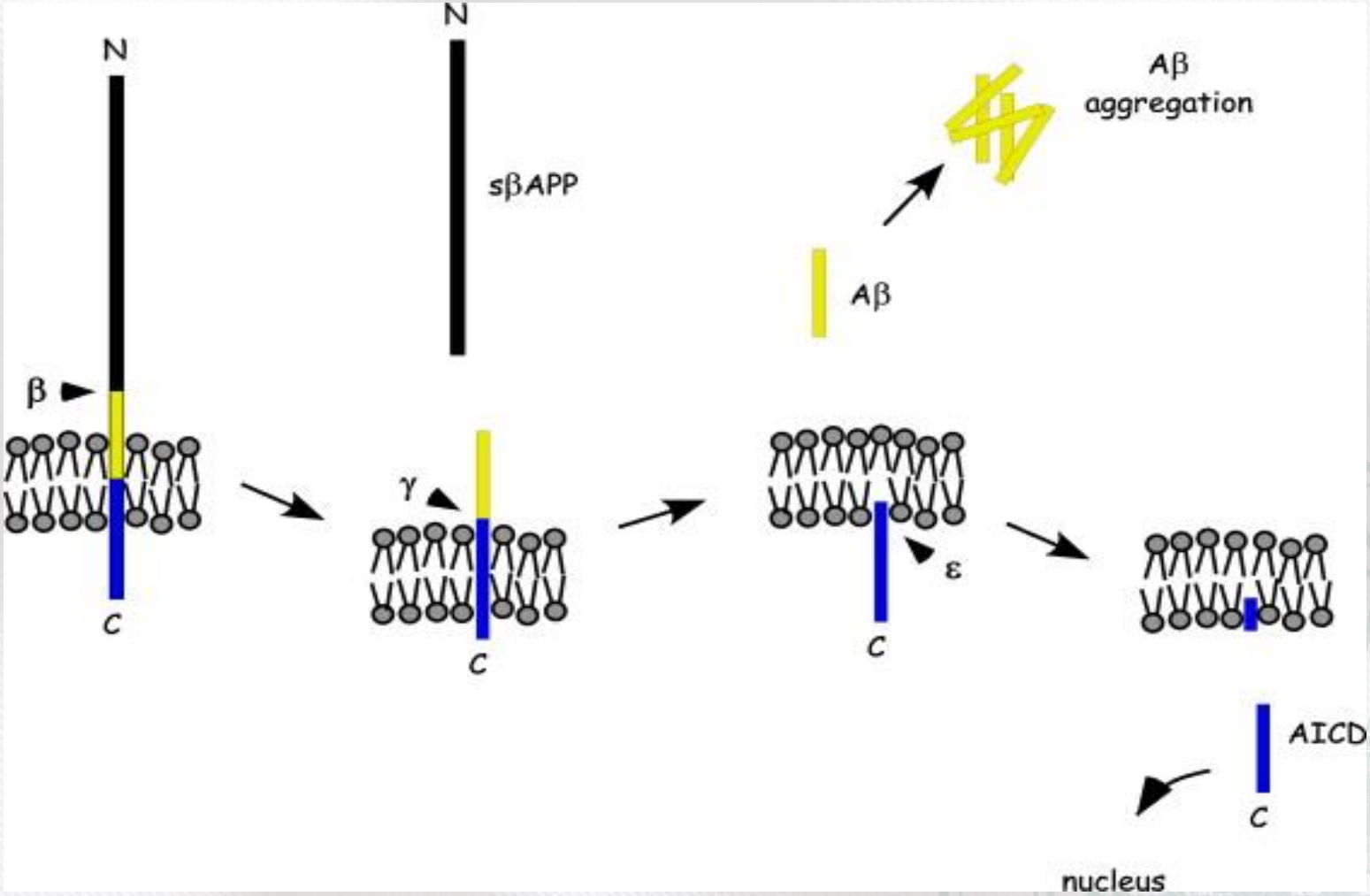
specific patterns on functional neuroimaging with PET scans

proven autosomal dominant mutation within the immediate family

Pathology

- **Senile plaques** are one of the major neuropathological hallmarks of AD. They are formed as a result of excessive amyloid β ($A\beta_{42}$) production, aggregation, and deposition in the brain.
- $A\beta_{42}$ is formed after processing the amyloid precursor protein (APP) through the amyloidogenic pathway.

APP and the amyloidogenic pathway



Pathology

Tau is found in microtubules of neuronal axons. Tau proteins are an integral part of transport of nutrients, growth, and stability of axons.

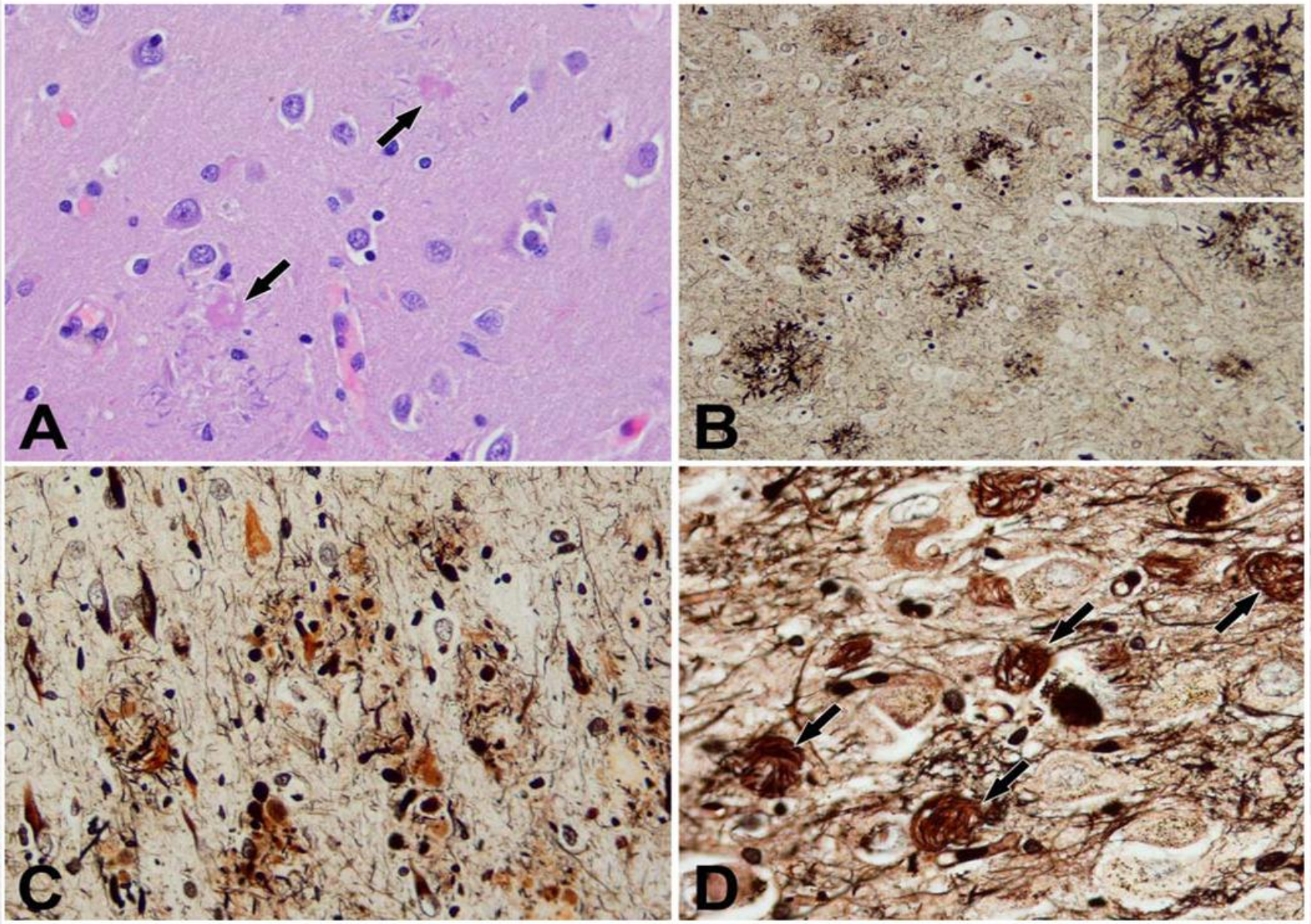
Tau is a major component of **neurofibrillary tangles-** the other neuropathological hallmark of AD.

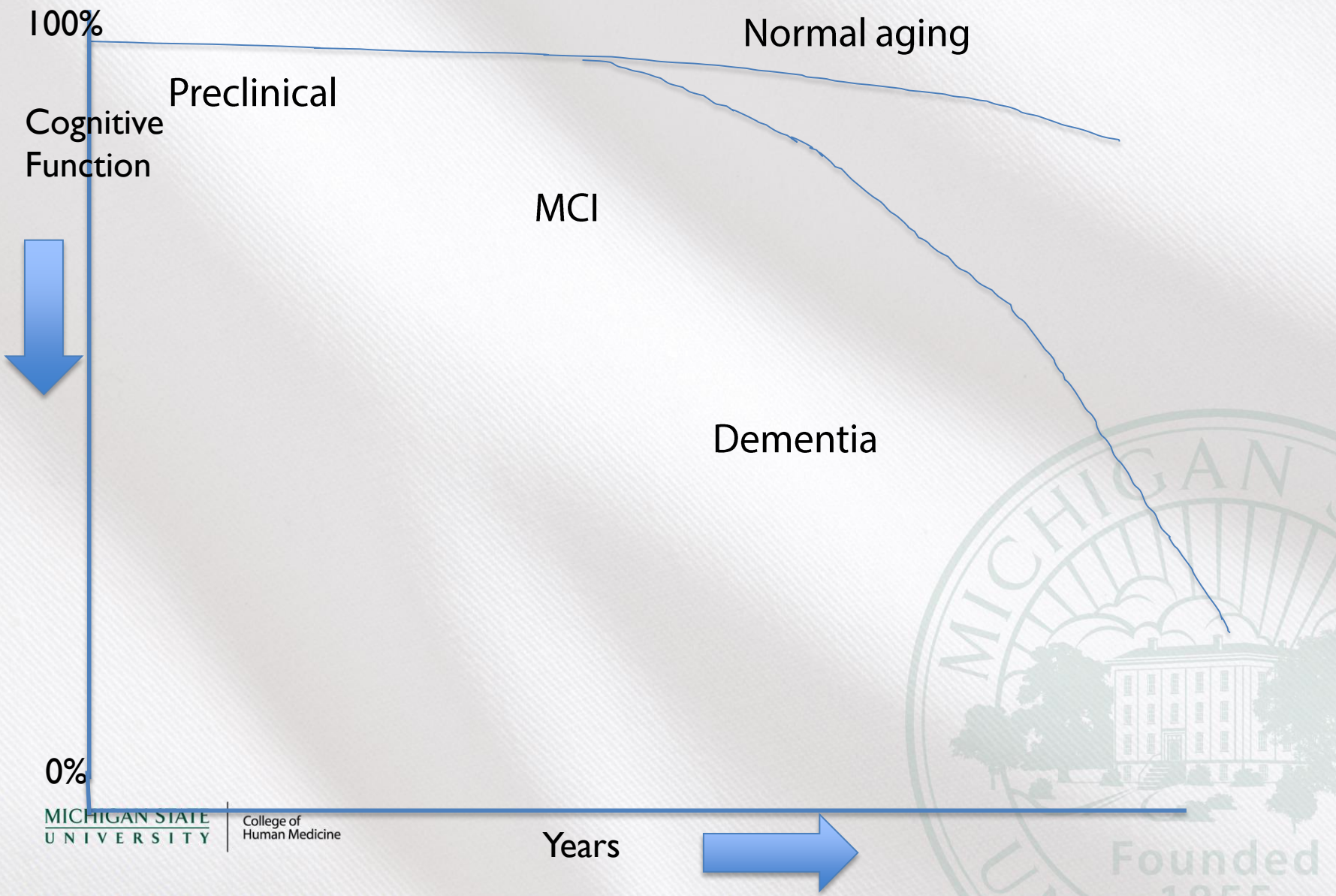
Hyperphosphorylation of tau (p-tau) leads to detachment of tau from microtubules, degradation of microtubules, degradation of axons and neuronal death.

Axonal death leads to the release of tau into CSF

CSF t-tau, p-tau levels elevated in AD

AD Pathology Senile plaques + Neurofibrillary tangles




100%
Normal aging
Preclinical
Cognitive Function
MCI
Dementia
0%
Years

In the beginning

Risk Factors:

- Genetics
- Lifestyle
- Cardiovascular status
- X factor

Genetics

APOE - the most prevalent brain lipoprotein, 3 alleles- 2,3,4

Genetic and epidemiological studies revealed that the risk of developing AD is 2-3 fold higher in people with one APOE ε4 allele and about 12-fold higher in those with two APOE ε4 alleles

APOE is deposited in neuritic plaques and neurofibrillary tangles

Structural MRI experiments revealed accelerated age-related decreases in cortical thickness and the hippocampal volume of healthy APOE ε4 carriers

Genetics

Maternal / Paternal	APOE ε2	APOE ε3	APOE ε4
APOE ε2	Normal risk	Normal risk	2-3 X HIGHER
APOE ε3	Normal risk	Normal risk	2-3 X HIGHER
APOE ε4	2-3 X HIGHER	2-3 X HIGHER	12 X HIGHER

Lifestyle

Body Mass Index (BMI)

Is a person's weight in kilograms divided by the square of height in meters

overweight = BMI of 25-29

obesity = BMI of ≥30

Lifestyle

Being overweight (BMI 25-29) at age 40–45 increased ones risk of developing dementia by 35%

Being obese (BMI > 30) in middle age increases the risk of developing dementia to 74% when compared to normal weight individuals.

Epidemiological studies have shown that obesity in middle age (40-50 years old) increases the risk of developing dementia and Alzheimer's disease, irrespective of associated medical conditions such as diabetes or vascular disease

Increased levels of plasma amyloid proteins have been found in a number of studies of obese individuals suggesting a possible mechanism linking midlife obesity with the later development of Alzheimer's disease.

Animal data on lifestyle

Obesity-induced blood–brain barrier damage is associated with microglia activation, upregulation of activating Fc-gamma receptors and proinflammatory cytokines, and increased oxidative stress in mice

Diet-induced obesity is consistently associated with an increase in cerebral amyloid pathology in mice models of Alzheimer's disease.

Lifestyle

Epidemiological data support an inverse relationship between the amount of physical activity undertaken and the risk of developing AD

Regular physical activity increases the endurance of cells and tissues to oxidative stress, vascularization, energy metabolism, and neurotrophin synthesis, all important in neurogenesis, memory improvement, and brain plasticity.

Diet

The Mediterranean-like diet includes high intake of vegetables, legumes, fruits, cereals, fish and monounsaturated fatty acids such as olive oil; low intake of saturated fatty acids, dairy products, meat and poultry; and mild to moderate amounts of alcohol.

A recent study found that people following a Mediterranean-like diet had a larger brain volumes than people who did not follow a Mediterranean diet.

The study does not prove that the Mediterranean diet prevents brain shrinkage; it shows an association.

Cardiovascular

A study investigated the relevance of the Framingham cardiovascular risk profile (FCRP) in influencing cognitive deterioration in a population of Alzheimer's disease (AD) patients.

n = 284 patients with AD

Findings show that FCRP can predict the progression of deterioration in AD patients. This was particularly evident in patients with major genetic (APOE ε4) and atherosclerotic risk factors.

Preclinical

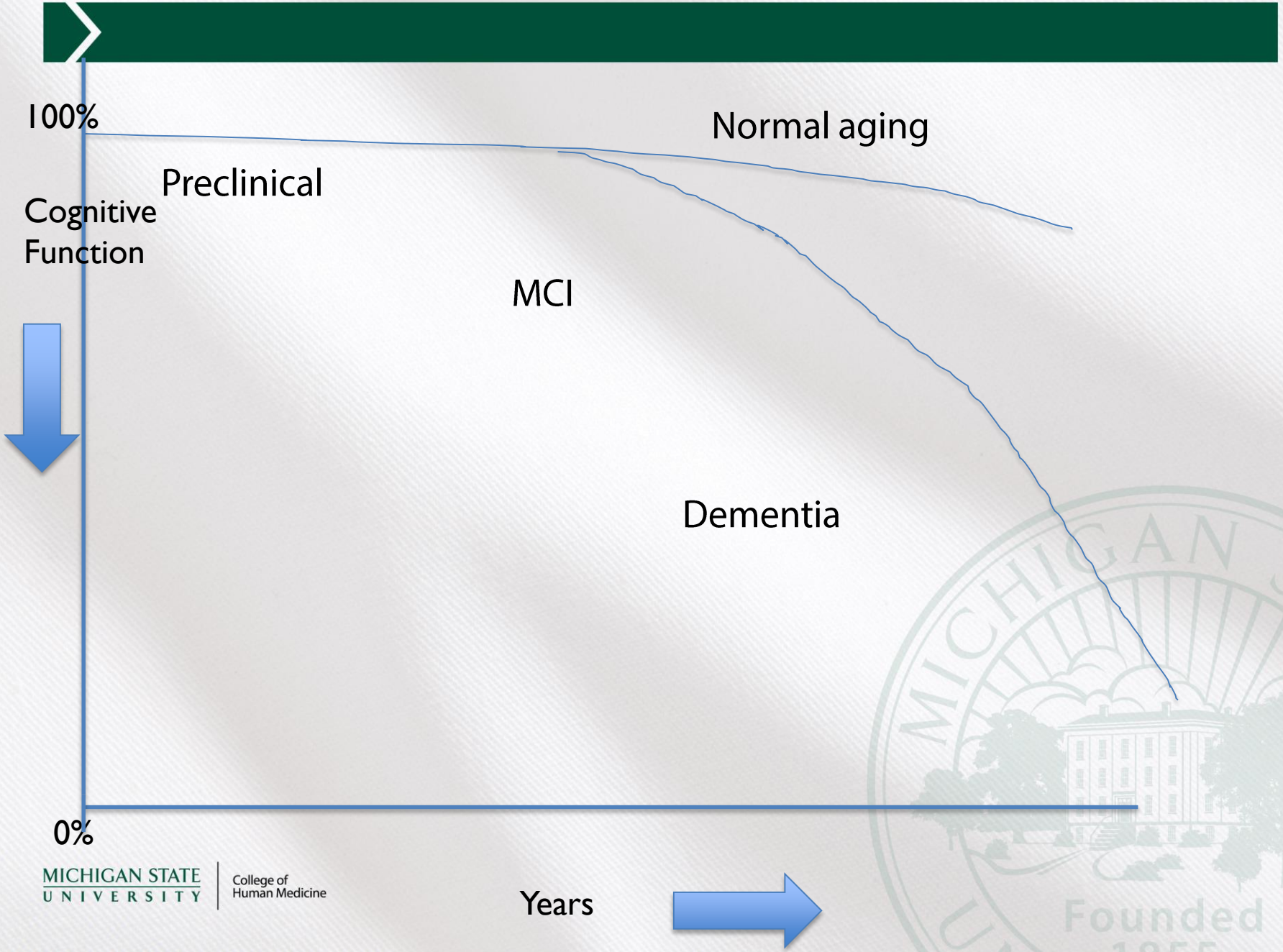
Honolulu Health Trial

Diagnose PD 20-30 years before clinical symptoms apparent

Huntington's disease

DNA test makes the diagnosis 20-30 years before clinical symptoms appear

What about AD?



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Biomarkers: Cerebral spinal fluid

There is now convincing evidence that CSF Aβ42 and tau levels convert from normal to "pathological" levels **years** before the onset of clinical symptoms.

Changes in CSF Aβ42 can be appreciated **25 years** before expected onset of clinical symptoms- Possible biomarker for AD?

Changes in CSF tau levels rise **15 years** before expected onset of clinical symptoms. Possible biomarker for AD?

Biomarkers: Cerebral spinal fluid

Aβ42 Low CSF (< 500pg/mL)

high sensitivity (78-100%) for AD

low specificity (50-80%) for AD

Aβ42 low CSF levels seen in FTD, PDD, LBD, VaD, CJD, MSA

tau levels in CSF is sensitive (84%) and specific (91%) in differentiating AD vs normal aging

Biomarkers: Cerebral spinal fluid

CSF biomarkers have also showed good sensitivity (83–95%) and specificity (71–90%) in predicting which subjects with mild cognitive impairment (MCI) will progress to AD

Biomarkers: Cerebral spinal fluid

High levels of t-tau is not specific for AD, as elevated t-tau seen in stroke, VaD, FTD, CJD, TBI

Phophorylated tau (p-tau) is increased two fold in AD

p-tau has >80% specificity differentiating AD from other forms of dementia

Biomarkers: Cerebral spinal fluid

"AD signature" consisting of low CSF Aβ42, elevated CSF t-tau and elevated p-tau

"AD signature" demonstrates 80–95% sensitivity and specificity in identifying subjects with AD in the dementia phase of disease

CSF ratio Aβ42 / p-tau is the most sensitive and specific for AD

Biomarkers: Serum

APOE ε4

- Serum
- Reliable

Biomarkers: Serum

Two Tau neo-epitope fragments: an ADAM10-generated fragment (Tau-A) and a caspase-3-generated fragment (Tau-C) are worth studying as possible serum biomarkers for AD.

Tau-A and Tau-C were able to separate subjects with (AD and MCI) from those with other dementias

Tau-A showed a significantly greater discrimination between AD and MCI subjects and patients with other dementias when compared to CSF biomarkers t-tau and p-tau

Biomarkers: Serum

Four miRNAs (miR-31, miR-93, miR-143, and miR-146a) were markedly decreased in AD patients' serum compared with controls

The panel of miR-31, miR-93 and miR-146a can be used to discriminate AD from VaD

CSF Biomarkers: Limitations

20% of cognitively normal subjects:

- low CSF Aβ42 levels
- positive (abnormal) PET scans.

6% of subjects with dementia:

- normal CSF Aβ 42 levels
- negative (normal) PET scans

CSF Biomarkers: Limitations

CSF biomarkers do not provide insight into the topographic distribution of pathological changes in the brain.

Aside from small increases in CSF t-tau, the biomarkers remain fairly stable during the dementia phase of disease

CSF biomarkers for AD are helpful in diagnosing AD but have limited utility in disease staging, prognosis or response to treatment.

Medicare dose not pay for CSF tau or Aβ2 levels

Serum Biomarkers: Limitations

Serum APOE ε4

- Medicare does not pay for testing
- Positive predictive value

Serum Biomarkers: Limitations

Despite being the focus of intense investigation, the utility of **serum** Aβ as AD biomarkers has not been fully defined.

Serum Aβ42 levels in AD show considerable overlap with non-AD controls

X Factor

Associations

Origins

RECAP

- Changes are taking place years before the clinical onset of symptoms
- Looking for biomarkers in the asymptomatic stage
- Looking at the very onset of the degenerative process
- Genetics, lifestyle do make a difference

Biography

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LOCAL RESOURCES

Dementia in West Michigan

RETHINKING DEMENTIA
Accelerating Change

INFORMATION ABOUT DEMENTIA

Alzheimer's Association

- Articles, videos, 24/7 helpline
- Incorporates other dementias, not just Alzheimer's
- www.alz.org, 1-800-272-3900

Dementia Friendly Grand Rapids

- www.dementiafriendlygr.com

Caregiver Resource Network

- www.caregiverresource.net

Youtube videos – search!

RETHINKING DEMENTIA
Accelerating Change

CAREGIVER EDUCATION

Alzheimer's Association

- Educational classes for caregivers (any type of dementia)
  - General Alzheimer's series
  - Dementia-related behaviors
  - Dementia conversations
- Offered at various locations, $10 suggested donation per class
- Online information, education, and practice recommendations
- www.alz.org, 1-800-272-3900

Family Caregiver University

- Monthly classes, suggested $5 donation
- Fall prevention, Understanding dementia, Healthy eating and dental care, Home maintenance….
- At the Area Agency on aging of Western Michigan
- www.familycaregiveruniversity.org

RETHINKING DEMENTIA
Accelerating Change

IN-HOME ASSESSMENT

Independent Living Program (Occupational Therapy)

- Assessment, education, and recommendations to increase functional independence
- Provided by Easter Seals, www.mieasterseals.com, 616-942-2081
- Funded by Kent County Senior Millage, so fees are based on income

Stepping Stones (Recreation Therapy)

- Assessment, therapy, and education to address physical, social, cognitive, and emotional conditions to increase independence
- Provided by Life Therapeutic Solutions, www.life-ts.com, 616-828-5492
- Funded by the Kent County Senior Millage, so fees are based on income

Choices for Independence

- Assessment, education, and care planning
- Provided by the Area Agency on Aging of Western Michigan, www.aaawm.org, 616-456-5664

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CARE MANAGEMENT

Reliance Community Care Partners

- www.relianceccp.org, 616-956-9440

Area Agency on Aging of Western Michigan

- www.aaawm.org, 616-456-5664

Local Home Care Agencies

RETHINKING DEMENTIA
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SUPPORT GROUPS

For people with dementia

- Early-stage dementia discussion and support group
- Younger onset dementia support group

For caregivers

- Adult children of a person with dementia
- Dementia caregivers
- General caregiving support

Find the list and contact information at

www.caregiverresource.net/support_groups or by calling 616-456-5664

RETHINKING DEMENTIA
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INFORMATION AND ASSISTANCE

Alzheimer's Association

- www.alz.org/gmc
- 24/7 helpline 1-800-272-3900

Area Agency on Aging of Western Michigan

- www.aaawm.org
- 616-456-5664

RETHINKING DEMENTIA
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Question & Answer

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Please visit the resource table on your way out.