

Sutter Neuroscience Institute

The 27th Annual Sutter Neuroscience Symposium

Friday & Saturday, January 27th & 28th, 2012

Silverado Resort, Napa



Memory, MCI, and Alzheimer's 2012

William J. Au, MD
Director of Adult Neurology
Sutter Neuroscience Institute

Case studies in dementia: an exercise
in differential diagnosis.

New guidelines for the diagnosis of AD

Promising clinical trials

Dementia Case Studies

Case 1

74 y/o retired physician presenting with falls, apathy, depression, STM loss, REM sleep problem, visual hallucinations of people when he sees shadows (onset 1 year ago)

Drives, and handles finances, ADL's intact

Exam: mild bradykinesia, deliberate speech, some increase tone in extremities, MMSE 25, 0/3 delayed recall, missed 2 in spelling "world" backward. Trouble putting numbers in clock

Case 1

MRI brain with mild atrophy, hippocampi normal, question of a few hypodense areas raising concern of strokes

Labs normal.

Differential diagnosis: VD, AD, LBD, FTD, Parkinson's with dementia, major depression

Case 1

Dx: DLBD

Good initial response to ACHEI

Memantine with no benefit

Mild symptomatic benefit with SSRI and
antipsychotics, carbidopa-levodopa

Fluctuating course with continued
progression of dementia

Case 1

Second opinion: DLBD

FDG-PET suggestive of FTD

Pathological Diagnosis (autopsy)

DLBD

Very little amyloid plaques and NFT's

No infarcts

Diffuse Lewy Body Disease Diagnostic Criteria

Central Features

Progressive dementia

Core Features

Fluctuating cognition

Recurrent visual hallucinations

Parkinsonism

DLBD

Suggestive Features

REM sleep behavior disorder

Increased sensitivity to neuroleptics

Low dopamine transport uptake in
basal ganglia

(DatScan with Ioflupane, sensitivity
88%, specificity 100%)

DLBD

Supportive Features

Repeated falls

Frequent LOC

Autonomic dysfunction

Hallucinations in other modalities

Visual-spatial abnormalities

DLDB

Probable Diagnosis

Dementia plus 2 or more core features or
Dementia plus one core and 1 or more
suggestive features

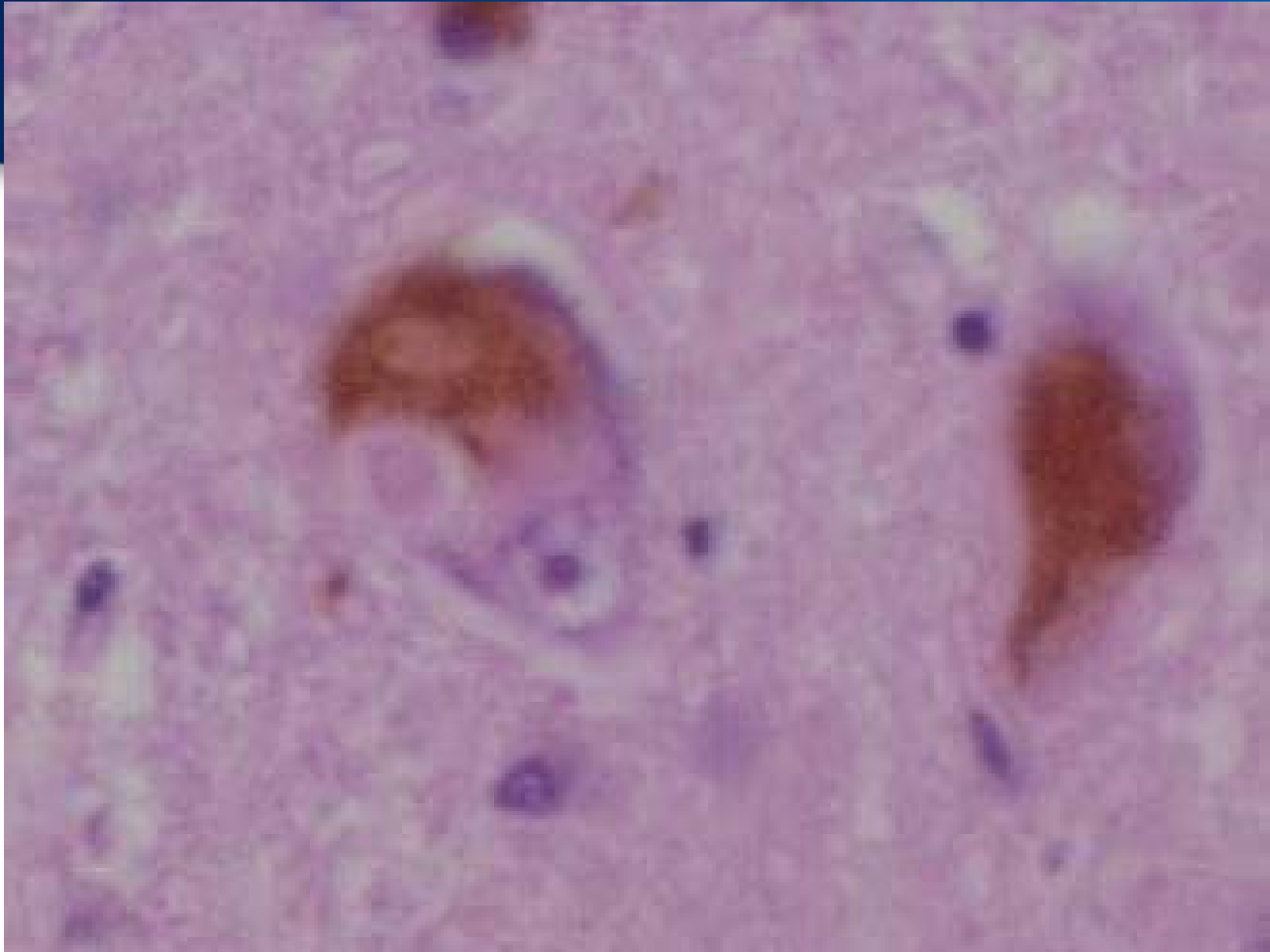
Possible Diagnosis

Dementia plus one core feature or
Dementia plus one or more suggestive
feature

DLBD pathology

Lewy bodies (intraneuronal) contain aggregates of alpha-synuclein, a small protein of unknown function, and ubiquitin. Missense mutations of the gene encoding synuclein is associated with early onset autosomal dominant Parkinson's. Cortical and subcortical deposits are seen in DLB, in glia in MSA leading to the some to coin the term "synucleinopathy" for these disorders.

DLBD also has plaques and NFT in the brain, but much less than in AD, though more than controls
LB may be seen in AD in late stages



Case 2

Mr, D.B. is a 59 year old man, a consultant for the State Dept. of Education, seen in 1/2010 for concern with STM loss over 1-2 years. Seemed more withdrawn and “spacey” at times.

Exam normal. MMSE 29, brain MRI normal, Neuropsych testing with mild delay is processing speed, depression, cognitively “normal”

Responded well to Citalopram

FH: Father age 90 with mild dementia. Sister died of ALS.

Case 2

2/2011, one year later, he presented with loss of appetite, libido, becoming more impulsive, short term memory worse, job performance began to suffer

Exam: affect blunted, depressed, detached, no muscle weakness or Parkinsonism

Study ordered

Case 2

FDG-PET revealed bifrontal hypometabolism, left more than right

Trial of Namenda without benefit

5/2011

weight loss worsen, some trouble swallowing, losing coordination of hands

Exam: Atrophy of intrinsic muscles of both hands, weakness in arms and bulbar muscles

Dx:FTD with MND (ALS)

Frontotemporal Dementias

Consensus nomenclature 1994

Pick (25%) and non-Pick forms (75%)

Prevalence: 3 to 8% of all dementias, 10% of those that died before the age of 70

Average age on onset 54 ± 7.6 (45-70)

Average age of death 64.3 ± 8.1 (51-77)

Family history: Up to 40% of patients with FTD show a FH of dementia or related condition such as Parkinsonism or ALS, but only 10% are clearly autosomal dominant.

FTD with Behavioral Changes (BvFTD)

The most common signs and symptoms involve extreme changes in behavior and personality

Increasingly inappropriate actions

Loss of empathy and other interpersonal skills

Lack of judgment and inhibition

Apathy

Repetitive compulsive behavior

A decline in personal hygiene

Changes in eating habits, predominantly overeating

Lack of awareness of thinking or behavioral changes

FTD with Speech and Language Problems (LvFTD)

Primary progressive aphasia is characterized by an increasing difficulty in using and understanding written and spoken language.

Subtypes:

Progressive non-fluent Aphasia (PNFA)

Semantic Aphasia

Progressive non-fluent Aphasia (PNFA)

Hesitant, effortful speech

Speech '**apraxia**'

Stutter(including return of a childhood stutter)

Anomia

Phonemic **paraphasia**(sound errors in speech e.g. 'gat' for 'cat')

Agrammatism (using the wrong tense or word order)

Mutism

Semantic Aphasia

Difficulty generating or recognizing familiar words. For example, when a patient is shown a picture of a cat, he can neither name it nor can he recognize the word when it is provided. The patient characteristically asks “what is ‘cat’?” when it comes up in conversation or during testing. This happens for rare words first and common nouns for later stages. Verbs and abstract words are surprisingly spared.

Fluent spontaneous speech is retained. Especially in early stages, patients may be able to “talk around” the meaning of a specific word they are otherwise unable to generate. Word-finding pauses in speech become common, and patients have difficulty naming familiar objects.

Problems recognizing familiar objects and faces.

FTD with Movement Disorders or Motor Neuron Disease

Rarer subtypes of frontotemporal dementia are characterized by problems with movement or weakness, similar to those associated with Parkinson's disease or amyotrophic lateral sclerosis (ALS)

Signs and symptoms may include:

Tremor

Rigidity

Muscle spasms

Poor coordination

Difficulty swallowing

Muscle weakness

Muscle atrophy

Bradykinesia

FTD pathology

40% to 50% of FTLD are tauopathies (FTD-tau)-
Pick's (intraneuronal Pick Bodies), CBD, PSP
Tauopathy (Tau 55, 64kDa), different from AD
Absence of senile plaques, NFT, amyloid
angiopathy, Lewy bodies,

TDP-43 , tau negative, ubiquitin positive neuronal
cytoplasmic inclusions (FTD/ALS, LvFTD)

Case Study 3

83 y/o woman with STM problem for about one year. Examples include forgetting to turn off stove, leaving clothes in washing machine, forgetting appointments, where her husband parked the car in a parking lot. She pays the bills and balances the checkbook, prepares meals. She does not drive much due to peripheral vision problem from glaucoma.

Case Study 3

Mother had dementia

MMSE 25, 0/3 delayed recall, 8/10 orientation. Normal clock

CDR 0.5

MRI: mild generalized atrophy, Labs normal.

Dx: MCI-amnestic type

Mild Cognitive Impairment due to AD

- Cognitive change (per patient, informant, or clinician)
- Objective impairment (typically memory)
- Preservation of independence
- Not demented
- Rule out vascular, DLB, FTD, medical causes
- Evidence of longitudinal cognitive decline
- AD genetic factors APP, PS1, PS2, (increased risk with APOE 4)
- CSF biomarkers

Amestic MCI

Patients with **a-MCI** have been identified as a group at high risk of progressing to **Alzheimer's Disease** with a conversion rate of approximately **15% per year**.

Case Study 4

67 y/o practicing tax law attorney began having progressive trouble understanding speech, expressing self, finding words, and STM loss for 2 years. Drives to bay area daily for work. No personality changes or behavioral issues

Father had probable AD

Case Study 4

Exam with expressive fluent aphasia, anomia, knows meaning of words and chooses correct word when given multiple choices. MMSE 23, 0/3 delayed recall, problems with serial 7's and spelling. Clock: 3,6,9,12, unable to place hands.

General physical normal

MRI brain one year ago read as normal

Case Study 4

Logopenic aphasia: Slow speech, impair syntactic comprehension and naming, word searches, knows meaning of words. Pathology left posterior temporal cortex and inferior parietal cortex. It is variant presentation of Alzheimer's disease

Case Study 4

FDG-PET scan: marked abnormal bilateral posterior parietal decrease uptake of deoxy-glucose, together with less abnormal frontal and temporal involvement. Pattern compatible with AD

Neuropsychological testing: AD profile

Dx: AD, early age onset

Began treatment with donepezil, later memantine added.

New Guidelines for Diagnosis of AD

First revision in 27 years, NIA - AA,
4/2011

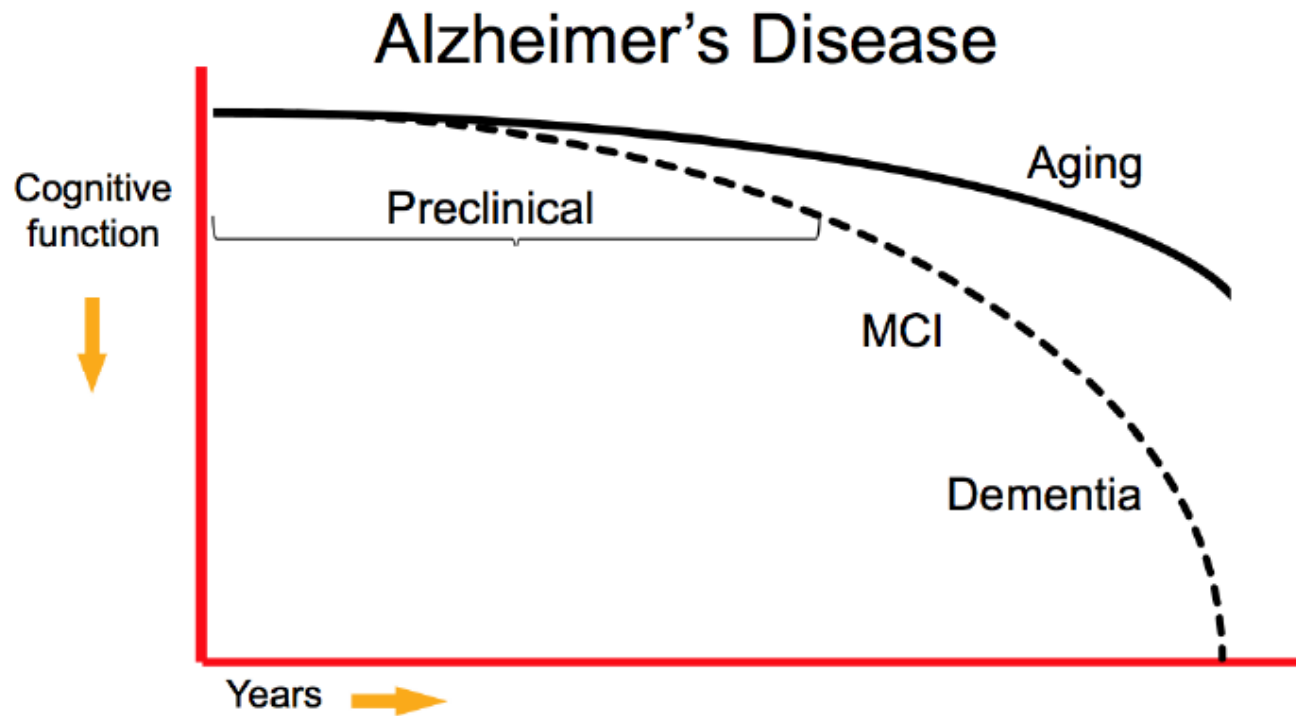
Preclinical AD

Biomarkers and imaging studies

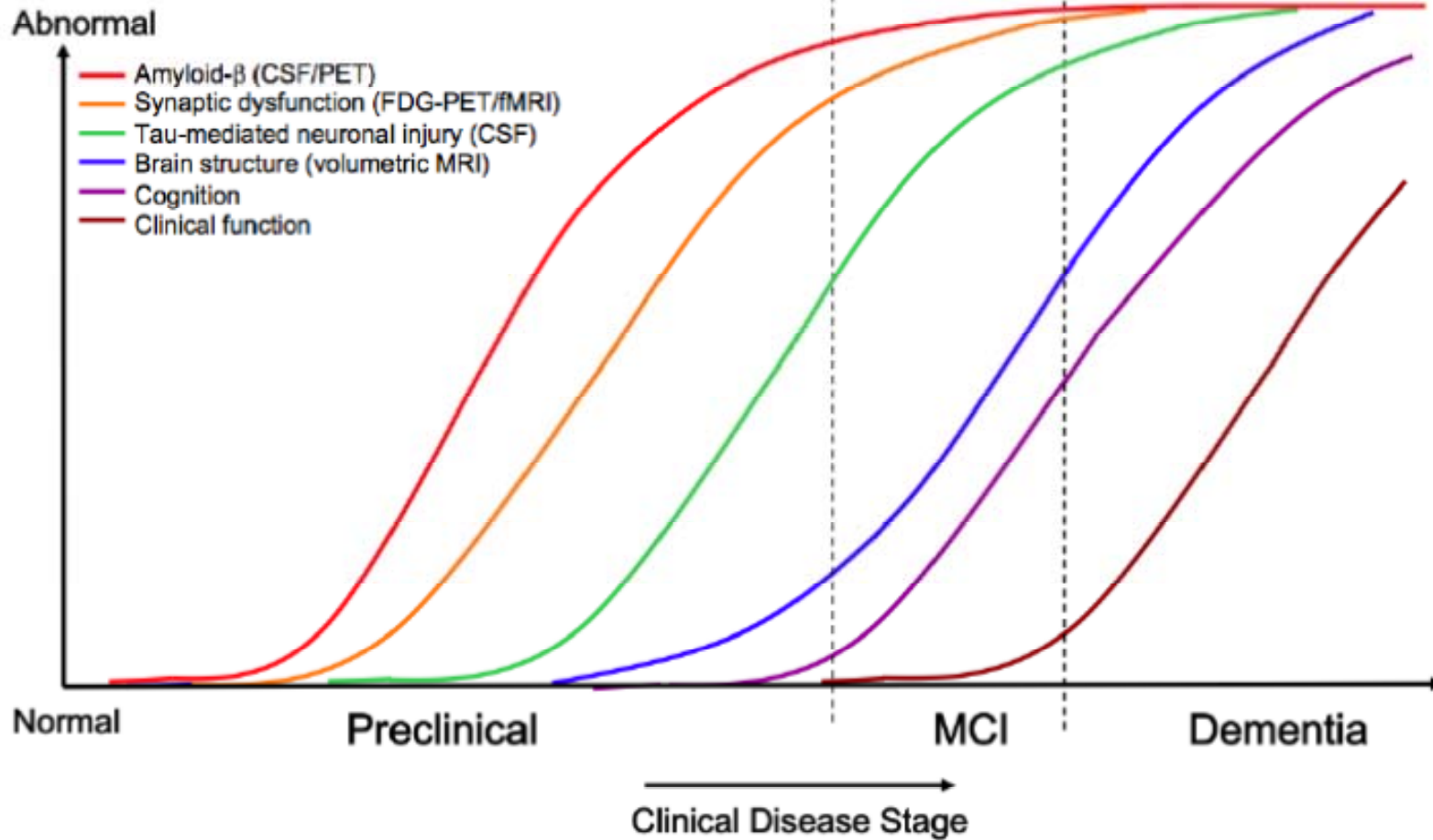
MCI (mild cognitive impairment due to
AD)

Dementia due to AD

The Continuum



Proposed Concept



Preclinical AD (research)

Stage I: Asymptomatic

Elevated amyloid PET with PIB or Avid 45/low AB42 in CSF

Stage II: Early neurodegeneration/synaptic dysfunction

Positive amyloid biomarker

Abnormal CSF tau or MRI or FDG-PET

Stage III: Symptomatic

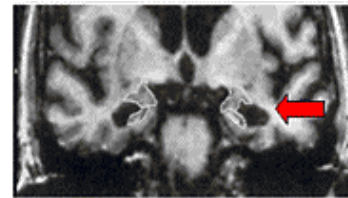
Stage II plus abnormal cognitive testing (does not meet MCI criteria)

Imaging

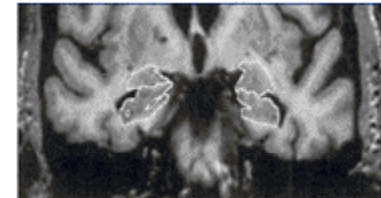
MRI

- Atrophy of hippocampus and entorhinal cortex

AD



Control

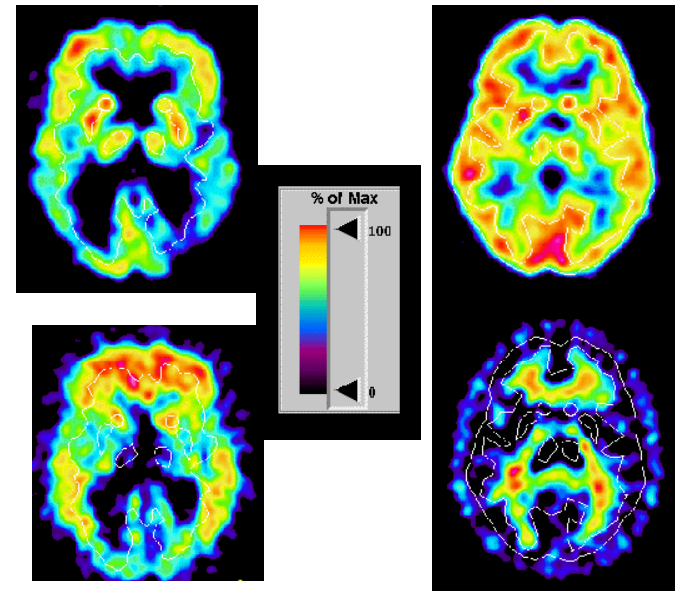


PET (FDG)

- Decreased tempo- parietal, posterior cingulate

PIB (marker of A β)

- Retention of PIB in tempo- parietal and frontal



Criteria for MCI (research)

MCI of a neurodegenerative etiology

Clinical syndrome consistent with MCI

Biomarkers not done or is ambiguous/neg

MCI of Alzheimer's type

Clinical syndrome plus topographic biomarkers
(MRI or FDG-PET)

Absent or ambiguous/neg molecular biomarkers

Prodromal Alzheimer's dementia

Clinical syndrome plus molecular biomarkers

Strengthened by topographic biomarkers, but neg
not exclusionary

Probable Alzheimer's Disease Dementia

Dementia

- A. insidious onset
- B. worsening
- C. initial and most prominent deficit:
 - a. **amnestic (most common)**
 - b. non-amnestic
 - language
 - visuospatial
 - executive dysfunction
- D. Probable should not be applied with substantial cerebrovascular disease, core features of Dementia with Lewy bodies, BV-FTD, SD, PNFA, other disease or medication that could have a substantial effect on cognition

Probable with increased level of certainty

- Documented cognitive decline on subsequent evaluations
- Genetic causation: APP, PSEN1, PSEN2. (APOE not sufficiently specific)

Possible Alzheimer's Disease Dementia

Meets all core criteria, except:

- Atypical course
 - More sudden onset
 - Not clearly progressive
- Mixed presentation
 - Concomitant cerebrovascular disease
 - Feature of DLB
 - Another disease or med that could effect cognition

Probable or Possible Alzheimer's Disease Dementia with evidence of the AD pathophysiological process

Optional clinical tools when deemed appropriate by the clinician

PET amyloid imaging

CSF

- Low beta amyloid 42
- Elevated tau and p-tau

FDG-PET

- Decreased uptake in temporoparietal cortex

MRI

- Atrophy in medial temporal and parietal cortex
- Particularly hippocampus



New Promising Clinical Trials

Intranasal Insulin Therapy for Alzheimer's Disease and Amnestic MCI

Archives of Neurology, Sept 12, 2011

Suzanne Craft, PhD, et al

Veterans Affairs Puget Sound and U. of Washington.

Intranasal Insulin Therapy for AD and a-MCI Archives of Neurology 9/2011

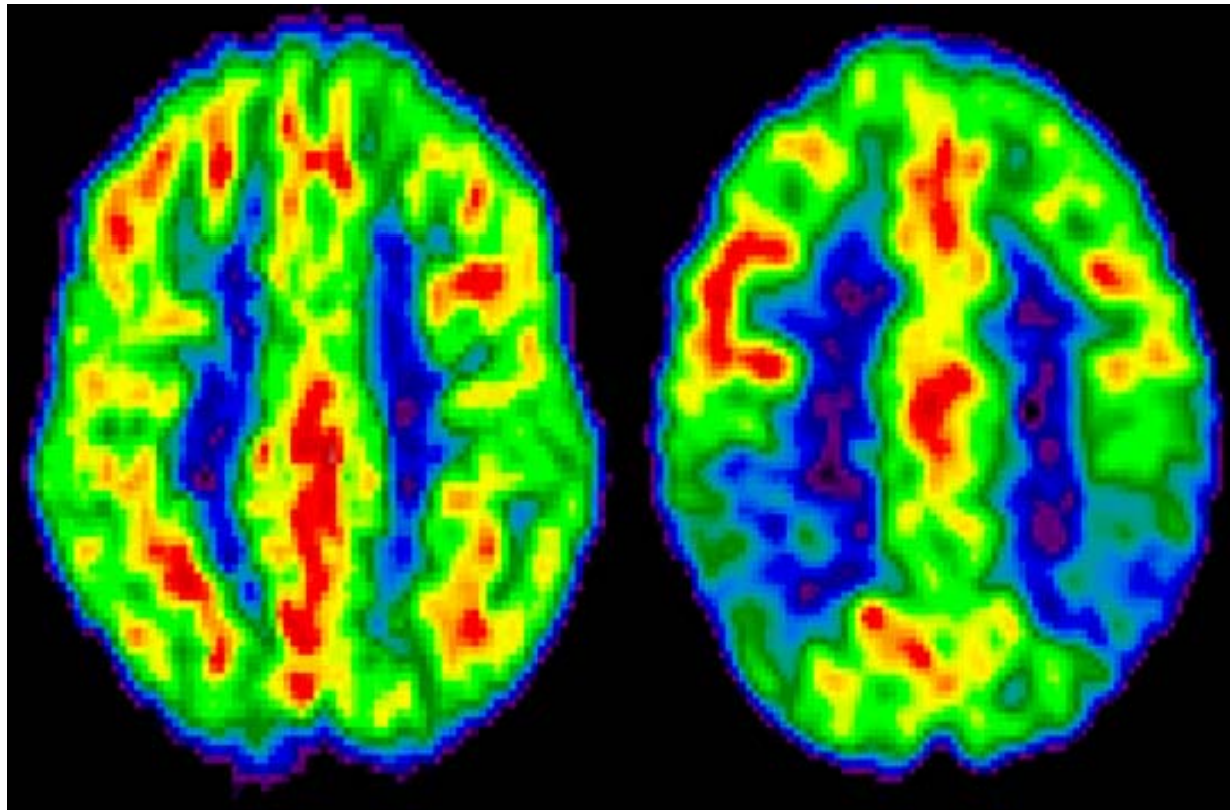
Rationale

Brain insulin receptors are densely located in hippocampus, entorhinal cortex, frontal cortex, in synapses.

Insulin levels and activity are reduced in AD : FDG-PET

Insulin modulates the level of AB

Typical AD PET Scan



Provided courtesy of M. Mega, MD, PhD,
Department of
Neurology, UCLA School of Medicine.

Intranasal Insulin Study

Study Design:

104 patients, 64 a-MCI, 40 mild-mod AD
(CDR 0.5-1, MMSE>15, some on ACHEI)

Three arms: 20U (10U bid) N:36, 40U (20U
bid) N:38, placebo N:30

Duration: Daily for 4 months

Primary end point: Delayed story recall,
DSRS (Dementia Severity Rating Scale)

Intranasal Insulin Study

Delayed Story Recall

A story containing 44 information bits read a single time to the participant, who then was asked to recall the story immediately and after a 20 minute delay

DSRS

Determined by a questionnaire completed by the study partner, rating change in cognitive, social, and functional status over time

Intranasal Insulin Study

Results:

20U group improved delayed story recall

20U and 40U preserved DSRS and ADAS-Cog, and ADCS-ADL scores for AD patients

Insulin groups had reduce progression of PET abnormality in substudy

No significant effect on CSF biomarkers levels in substudy

An Exploratory Study to Assess Treatment Effects of Intravenous Immunoglobulin (NewGam 10%) in Amnestic Mild Cognitive Impairment

Sutter Neuroscience Institute
Shawn Kile, M.D. and William Au, M.D.

Sponsors: Sutter Institute for Medical Research, Octapharma

IVIG

Commercial IVIG contain antibodies to AB
Ab in IVIG disassembled the fibril plaques by enhancing microglial migration leading to phagocytosis of AB (Istrin JNR Aug,2006))
Open-label study in AD subjects (Octagam 0.4g/kg daily x 3 days every 4 weeks for 6 months) showed a mean 3.7 point improvement in the ADAS-cog, CSF AB levels decreased by 30%,whereas serum AB levels increased (Dodel JNNP, Oct 2004)

IVIG

Relkin(Neurobiol Aging Feb 2008)

18 month open-label study using four dosing schedules of IVIG in mild AD subjects. All groups showed increase in serum AB with mean improvement of 2.5 points on the MMSE after 6 months and 0.5 points at 18 months (natural history of AD predicts 1.5 point decline per 6 months)

The group treated with the lowest dose of 0.4g/kg per week had the highest MMSE scores.

Phase II IVIG (Gammagard 10%) in mild to moderate AD Relkin

IVIG doses of 0.2 to 0.8 g/kg every 2-4 weeks for 18 months.

Significant decreased cognitive decline on the ADAS-Cog and decreased brain atrophy in subjects receiving early IVIG compared to the delayed treatment arm (placebo for 6 months then IVIG)

Ventricular Atrophy Maps



Placebo-treated Subject

IVIG-treated Subject

Ventricular Atrophy



Mild

Moderate

Severe

mean annual ventricular enlargement rate was 6.7% for those treated with IVIG vs 12.3% for those previously taking placebo. The rate of atrophy appeared to be lowest at a dose of 0.4 g/kg every 2 weeks (2.63%, $P = .048$).



Sutter Neuroscience Institute

A Sutter Health Affiliate

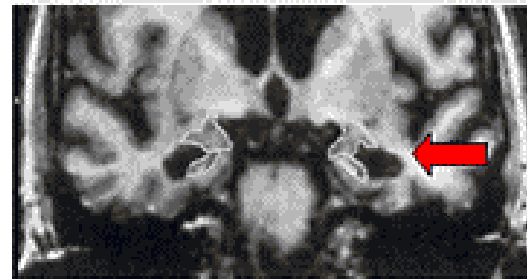
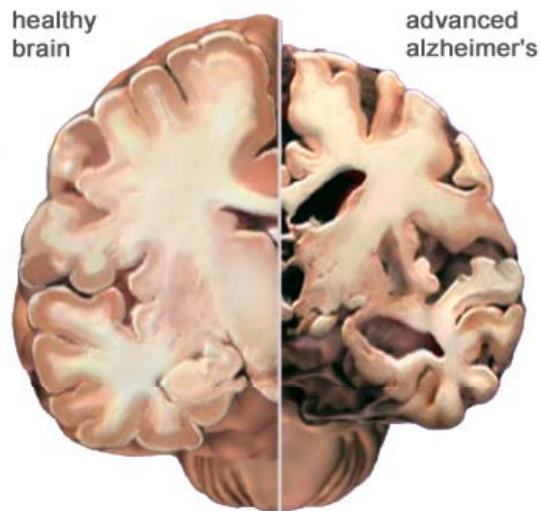
Ventricular enlargement rates were significantly associated with testing results on the Clinical Global Impressions of Change scale and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)

No treatment-related serious adverse events

Fillet et Al, July 2009

Retrospective analysis of the risk of AD and related disorders in people ≥ 65 with a prior history of one or more IVIG treatments. Cases were matched to controls on age, gender, and risk factors for AD. Analysis over a 4 year period showed previous treatment with IVIG was associated with a 42% lower risk of developing AD.

PREVENTION OF PATHOLOGY PRIOR TO DEVELOPING ALZHEIMER'S DEMENTIA



The potential protective effect of IVIG against Alzheimer's Disease could best be utilized in those at greatest risk for developing this type of dementia.

MCI-IVIG Study

This 2 year study will evaluate 50 subjects

- MRI brain volumetrics
- Cognitive testing
- preventing (or delaying) conversion to Alzheimer's disease
- CSF substudy

MCI-IVIG /study

Patients will be randomized to receive 10% IVIG 0.4g/kg Q2weeks for 5 infusions or placebo in a double blind fashion.

Follow-up visits will occur approx every 3 months for the duration of the study (24m after last infusion).

MCI-IVIG Study

Cognitive testing

- Neurological Exam, Clinical Diagnosis of Alzheimer's
 - NINCDS-ADRDA Criteria
- ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale)
- CDR-SB (Clinical Dementia Rating, Sum of Boxes)
- MMSE

CSF beta-amyloid protein 1-42/phosphorylated tau 181P biomarker mixture (analysis for Alzheimer disease signature)

MRI

- Screen
- 6wks after last treatment (IVIG or placebo)
- Conversion or 24m

Inclusion Criteria

Age from 50 to <85 years.

Diagnosis of Mild Cognitive Impairment,
Amnestic type (single or multi domain).

Mini-Mental State Examination (MMSE) score
of 24-30, inclusive.

IVIG-MCI trial

Contact information: Tammy Donnel,
study coordinator, SIMR

(916) 733-8930

Funding: Octapharma

SMC Foundation

Progress since initiation 1/2011

Target: 50 subjects with amnesic-MCI

Two arms: IVIG vs placebo, 1/1
randomization

As of Jan 2012

29 subjects enrolled and randomized

Thank You

