Early Diagnosis of Alzheimer’s:

How are we doing & Does it matter?

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Learning Objectives:

- Does it matter? – Of course it does!!
- How are “we” doing?:
  - Quick overview and latest advances in Alzheimer’s Disease
- Discuss Health care communities’
- Role, “Scope”, and “Hope!”
Does it matter?

"Who Cares?!" - Sophie (Estelle Getty) In Golden Girls:

- TNF inhibitor Etanercept s/c showed good safety profile in a small gp. of patients with mild to moderately severe AD.

  "some interesting trends favored etanercept"

There were no statistically significant changes in cognition, behavior, or global function

  - Butchard, J Et al. Neurology 2015 May 26; 84:2061

?? Too Little To Late??

TNF is an immune signaling molecule produced by glia and neurons and also macrophages (FDA approved in refractory RA ), in the brain it regulates synaptic communication. Its effect in hippocampus is important. Excess TNF is present in CSF of pt.s with AD – it is therefore implicated as a mediator of synaptic dysfunction
Does it matter?–Of course it does! “so we use resources correctly”

- Rate of hospitalization for "ambulatory care-sensitive conditions" is significantly higher among individuals who were diagnosed with dementia (86%) than those that remained dementia free (59%) Phelan EA et al Association of incident dementia with hospitalizations: - JAMA 2012 Jan 11; 307:165.

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Does it matter?–Of course it does!

- “so we use resources correctly” ? Sure but -

- In primary care settings, fewer than 50% of patients with dementia are diagnosed

# Current Numbers of those diagnosed from TN state are in the public domain are astounding as well
Does it matter? - Of course it does! So face the “Elephant in the Room”

Because there is the critically important psycho-socio-economic driver for early diagnosis

- Diagnosed early, patients/families can put Affairs In Order and Make Early Decisions

STOP FUSSIN AND GET ON WITH IT!!
”We didn’t have the opportunity 65 years ago!!”
Understanding Dementias

- Alois Alzheimer described (AD) in 1902
- It is the Most common form of dementia
- Augustine Deter died at age 53!!

Today-
- This progressive neurodegenerative disorder is affecting >37 million people worldwide and is increasing in incidence based on its primary risk factor, which is ADVANCING AGE------

Dementia - disease burden

- Aggregate healthcare expense on Dementia in 2011 was estimated at: $183 Billion
- On present trajectory by 2050 this cost is projected to rise to 1.1 Trillion $
- In 2011 Congress==>President signed NAPA - the “national AD project act”
While memory concerns predominate, patients with AD often experience language and visuospatial dysfunction in addition to neuropsychiatric symptoms such as anxiety, depression, apathy, and agitation – in reality a continuum.

**AD – definition:**
Gradually progressive cognitive and behavioral disturbance that represents decline from prior level in 3 or more areas of cognitive function, not due to other medical or psychiatric illness.

- Insidious episodic memory impairment ➔ chronic progression
- Multiple cognitive defects
- Significant impairment in social or occupational function

-McKhan et al 1984
Laboratory Tests in the Diagnosis of Dementia

(AAN Practice Parameter ’01)

- CBC, electrolytes, glucose, BUN/creat
- LFTs, TFTs, ESR
- B12 level
- Depression screening
- CT or MRI scan

Rationale for doing above tests?

<table>
<thead>
<tr>
<th>EXCLUDE TREATABLE CAUSE</th>
<th>TESTS INDICATING AD</th>
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<tbody>
<tr>
<td>A positive yield is uncommon but a “pleasant surprise” if does occur</td>
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<tr>
<td>List can be expanded if clinically something “DOES NOT FIT” – is it that or our clinical skills to be blamed!</td>
<td></td>
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<tr>
<td>Regional atrophy on MRI</td>
<td></td>
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<tr>
<td>But causes of atrophy can be many</td>
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Other MRI Scanning techniques:

**MRI VOLUMETRY**
- Used in some centers – not routinely performed with rigor with which this technique could be utilized

**DTI**
- “work in progress

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Defining Pathological Features-
*synaptic & neuronal loss causing atrophy*

- Due to accumulation of plaques & tangles - major targets for drug discovery today

*Normal* | *AD* | *AP* | *NFT*
---|---|---|---
Seat of neuropathology

- Amyloid collects in between neurons 1st then NFTs begins accumulating in the entorhinal cortex, subsequently spreading to hippocampus amygdala and neocortex.
- There is cells loss in nucleus basalis of Meynert & the basal forebrain - structures responsible for most cortical cholinergic projections, thus resulting in cortical acetylcholine depletion, the most notable change in AD.
- Neurochemical dopamine, norepinephrine, and serotonin deficiencies have also been detected – smaller foot print

Treatment Options:

I. Cholinesterase inhibitors:
1. Donepezil
2. Galantamine &
3. Rivastigmine(Oral)
4. Rivastigmine(Transdermal)

II. NMDA antagonists: 5. Memantine
Regulates glutamate levels in brain reduce abnormal activity
5. Memantine- NMDA antagonist

Neither stop disease progression:

- Improve global function and cognition
- Reduction in behavioral disturbances
- Temporary stabilization of ADLs
- Delay nursing home placement
- Postpones worsening of symptoms for 6-12 months in 50% of patients
Clinical Progression of AD and MCI

**Time?**

- **MCI**
- **MMSE 24–30**
  - Mild subjective/objective memory loss
  - Normal function

- **Mild AD**
  - MMSE 20–23
  - Forgetfulness
  - Repetitive questions
  - Daily function impaired

- **Moderate AD**
  - MMSE 10–19
  - Progression of cognitive deficits
  - Short-term memory loss
  - Word-finding difficulties

- **Severe AD**
  - MMSE 0–3
  - Agitation
  - Altered sleep patterns
  - Total dependence: dressing, feeding, bathing

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Preclinical and Symptomatic AD

[Diagram showing progression from preclinical to symptomatic AD]

- CDR
- Neurological loss
- Tau
- Microglia
- Inflammation
- Ossative stress

Symptomatic AD
~7-10 y
What's New?!

New tests and New thoughts

Genetics and other tests became available:

- Testing is available for APOE and autosomal dominant AD - some pursue this option without seeking medical advice/ counseling
- CSF studies may help differentiate AD from inflammatory, infectious, or neoplastic causes of cog decline- sensitivity approaching 85%, specificity ~ 75% in the context of validation in patients with neuro-pathologic confirmation of disease. “Investigational biomarkers have yet to meet these stringent “ideal’s”
Amyloid imaging
- Pittsburg compound B (PiB), Amyvid (florbetapir)

- Amyloid burden increases as a function of 2 known risk factors of AD: Age and Epoe4

  - Fang et al. Neurology 2009; Morris et al ANN Neuro 2010

Other imaging tests have also been FDA approved or are being developed
Two meta-analyses & accompanying editorial highlight value of amyloid imaging as follows:

- Amyloid positivity may precede the onset of AD dementia by 20 to 30 years.
- Amyloid positivity may be the most valuable in supporting a diagnosis of early onset AD.
- Amyloid-negative imaging in dementia suggests a non-AD diagnosis at any age.

Cerebro Spinal Fluid biomarkers

**MARKER OF:**

**AMYLOID-BETA 1-42 ACCUMULATION**
- Paradoxical decrease in CSF amyloid-1B-42 as it is polymerizing and depositing in the brain.

**MARKER OF NEURONAL INJURY (NEURODEGENERATION)**
- CSF phosphorylated tau (p-tau) 181 and total tau are markers of neuronal injury; (increased levels seen in advanced disease).
- Combination of low csf AB1-42 & elevated csf P-tau indicates a biomarker signature of AD.
**NIA –AA Diagnostic Criteria for Alzheimer’s Disease**

- **Diagnosis**
  - Preclinical AD
  - Mild Cognitive Impairment due to AD
  - AD Dementia

- **Characteristic**
  - Asymptomatic, Biological evidence of AD pathology
  - Cognitive deficit with normal daily functioning, biological evidence of AD pathology
  - Typical history and symptoms with functional decline

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**International Working Group Criteria for AD-**

"No longer requires presence of dementia" - Hello!!

- Incorporates biomarkers
  - There are 2 Core Criteria-
    1.) Evidence of episodic memory loss
    2.) Biological evidence of AD:
    - Decrease in CSF abeta 42, Increase in Tau
    - Imaging: AD pattern FDG PET hypo - metabolism or atrophy; significant uptake with amyloid PET
- Known causative genetic mutation

What can CSF and Amyloid imaging, used together tell us?

- Strong inverse relationship between CSF a-beta42 and PIB amyloid burden

Conclusions

- Biomarkers are increasingly incorporated into diagnostic algorithms to increase confidence of diagnosis
- Field of biomarkers is rapidly evolving in response to
  - science/clinical studies
  - reimbursement
  - treatment option
  - standardization
In cases with normal cognition (n=336) from 4 autopsy cohorts, microinfarcts were the second most common pathology after Alzheimer’s disease, present in 1/3rd of cases.¹

- Microinfarcts are associated with cognitive impairment.²
  - Perceptual speed
  - Semantic memory
  - Episodic memory


White Matter Hyperintensities
Common in the aging brain but not a benign process

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<tr>
<th>Baseline</th>
<th>Year 4</th>
<th>Year 7</th>
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Evolution of white matter hyperintensities in a 51 year old woman with normal cognitive function over seven years
Kejal Kantarci M.D., M.S. Neuroradiology Mayo Clinic, Rochester, MN

Sleep! Being questioned to have a role in AD pathology
Mechanism Linking Sleep and Health

- In the laboratory setting, short-term sleep restriction leads to a variety of adverse physiologic sequelae, including
  - Impaired glucose control
  - Increased cortisol
  - Increased blood pressure
  - Sympathetic activation
  - Increased markers of inflammation
  - Decreased leptin level

- These data suggest that chronic sleep restriction may have long-term health consequences:

Population based studies


Sleep Markedly Increases Convective Exchange of CSF with Interstitial Fluid

Brain has no lymphatic draining system – how does it clear compounds?

Sleep Enhances Clearance of Beta-Amyloid

KX = ketamine/xylazine anesthesia


Conceptual Model

Yo-El Ju et al, JAMA Neurol, 2013
Sleep: Garbage truck for the brain!

Why we sleep?

- Metabolic-energy balance
- Immune/inflammatory
- Oxidative stress/free radical
- Protein folding, relief of ER stress
- Synaptic homeostasis
- Macromolecular biosynthesis
- Clearance of toxic waste
- ............

Debate as to whether sleep has a single core function or several simultaneous functions?

Function of sleep is for the brain and likely all tissues
Challenge

We worry about “Reversible Dementias”
Miss – Delirium (or acute confusional state)

- Depression – “Pseudo D”
- Delirium – the other “D”
- Endocrine Disorders
  - Thyroid disease
  - Vitamin B12 deficiency
- Other neurological disease:
  - Associated with Epilepsy
  - Occasionally other like HIV, like prion disease
  - Normal Pressure Hydrocephalus “NPH” - rare
Diagnosis:
informant corroboration of progressive episodic memory impairment is critical for diagnosis

- Early phase
  - Sphere of psychological dysfunction
    - Missed: Confusion with psychiatric disorders

- Middle phase
  - Sphere of cognitive dysfunction
    - Usually obvious
    - Missed: Confusion with functional or psychological disorders

- Late phase
  - Missed: Confusion with Neurological disorder

Question-
When did the mansion burn down?

- Atrophy began years before diagnosis of AD & is non-specific

- Autopsies shown profound layer-2 loss of entorhinal cortex neurons even in very mild AD or MCI with MMSC scores of >24!!
More than 80 different disorders cause dementia

- History and examination most informative
  - Symptom onset (sudden step-wise, insidious)
  - Clinical course (stable or progressive, rapid / slow)
  - Initial and predominant symptoms
  - Pattern of cognitive deficits (domains)
  - Findings on Neurological examination
- Medical Illness- blood tests
- Brain imaging, sometimes CSF, EEG, biopsy

Proposed Risk Factors For AD?

- Age & Genetic (most robust data): May account for much (60%) of the variability in the development of AD. ApoE increases risk 3 to 10 fold; only about 5% of genetic cases associated with identified genes in an autosomal dominant inheritance pattern.
- Medical factors: Associated-HTN, DM, Metabolic syndrome; Hyperlipidemia. Also (but poorly studied) – GSA, obesity; head trauma.
- Late life depression; Social isolation also associated with cognitive decline.
- Tobacco & excessive alcohol: Current smoking.
- Medications: statin drugs; anti-HTN; anti-inflammation.
- Physical activity & leisure: ?
Conclusion:

- Some advances in genetics, biomarkers for early disease detection and assessment of disease progression, and novel therapeutic strategies to modify the natural history of the disease are compelling.
- There is need of further study before its implementation into routine clinical practice is feasible.


Most common presenting symptom is insidious episodic memory impairment, often involving names of persons or objects. Pt. often experiences language and visuospatial dysfunction in addition to neuropsychiatric symptoms (anxiety, depression, apathy, agitation). This is reflected in AD pathology— in the neuro anatomically vulnerable basal forebrain and medial temporal structures which then spreads to involve posterior cingulate gyrus, temporal neocortex and the parietal lobes.
Take Home points:

- Be objectively vigilant to change.
- If you sense it is happening it is possible that you are right! whether you are a caregiver or the victim!! “believe in your gut.” Be willing to challenge us we will learn from you and from each other. That’s the ONLY way!
- There is urgent need to aggressively treat vascular risk factors at all ages
- We all need to learn how to “buy sleep” and know the currency with which to buy it!