DEMENTIA
DIAGNOSIS AND TREATMENT
WHY CARE?

• Dementia affects everyone, young and old.

• Between 2000 and 2014, there was an 89 percent increase in deaths due to dementing illnesses.

• In 2016, more than 15 million unpaid caregivers provided an estimated 18.2 billion hours of care valued at over $230 billion.

• 2017 marks the first time total payments for caring for individuals with dementing illnesses will surpass a quarter of a trillion dollars.
DEMENTIA

Memory loss is **not normal** in the older adult.

Dementia is a blanket term that is used when talking about memory loss that is associated with a decline in function.

**DSM-V: Major Neurocognitive Disorder**
DEMENTING ILLNESSES

More specifically, Dementia is defined as:

- Memory impairment plus aphasia, apraxia, agnosia, and/or a disturbance in executive functioning

- Decline from a previously higher level of functioning

- Significant impairment in occupational or social functioning
IAGG BRAIN HEALTH CASE
FINDING

• Health Care Professionals need to know how well patients can follow instructions

• There are treatable causes of cognitive function

• Lifestyle interventions can slow the rate of cognitive dysfunction

• Early diagnosis allows development of advance directives
Early diagnosis and intervention can:

1) discover and treat a reversible cause of dementia
2) in some cases ameliorate or stall the disease process
3) help the person and his/her loved ones to plan for support services
4) allow the person to participate in advanced care planning
DEMENTIA

Use a validated instrument to help diagnose
- Saint Louis University Mental Status Examination
- Rapid Cognitive Assessment

Name the specific dementia type using clinical history, exam findings +/- brain imaging

Treatment should not begin until a diagnosis has been established.
Rapid Cognitive Assessment

ID#: ________  Sex: ________  Age: ________
Ethnicity (circle): African/Am  Asian  Caucasian  Hispanic  Non-Hispanic

1. Please remember these five objects. I will ask you what they are later.
   [Read each object to patient using approximately 1 second intervals.]
   Apple  Pen  Tie  House  Car

   Please repeat the objects for me. [If patient does not repeat all 5 objects correctly, repeat until all objects are recalled correctly or up to a maximum of 2 times.]

2. [Give patient pencil and the blank sheet with clock face.]
   This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o’clock.

   ___/2 (points) Hour markers okay
   ___/2 (points) Time correct

   [When scoring, give full credit for all 12 numbers. If the patient puts only ticks on the circle, prompt them once to put numbers next to those ticks for full credit. Do not repeat the time. When scoring the correct time, make sure that the minute hand points at the 10 and the hour hand points at the 11.]

3. What were the five objects I asked you to remember?

   ___/1 (point) Apple
   ___/1 (point) Pen
   ___/1 (point) Tie
   ___/1 (point) House
   ___/1 (point) Car
4. I’m going to tell you a story. Please listen carefully because afterwards, I’m going to ask you about it.

Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

What state did she live in?

__/1 (point) Illinois

[Do not repeat the story but do make sure the patient is paying attention the first time you read it to them. Do not prompt or give hints. The answer of “Chicago” as the state she lives in gets no credit but you may prompt them once by repeating the question when “Chicago” is given as the answer.]

____ Total Score [0-10 points]

<table>
<thead>
<tr>
<th>SCORING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8-10...................</td>
<td>Normal</td>
</tr>
<tr>
<td>6-7....................</td>
<td>Mild Cognitive Impairment</td>
</tr>
<tr>
<td>0-5....................</td>
<td>Dementia</td>
</tr>
</tbody>
</table>

RAPID COGNITIVE SCREEN VS MINICOG

AUC (95% CI)
RCS 0.98 (0.95-1.00)
Mini-Cog 0.92 (0.89-0.95)
IT IS NOT ENOUGH TO DIAGNOSE DEMENTIA...

- Rule out reversible causes
- Distinguish the dementia syndromes
- Provide complete bio-psycho-social care
Reversible Causes of MCI/Dementia

D: Drugs (digoxin, theophylline, cimetidine, anticholinergic)
E: Emotional (depression)
M: Metabolic (hypothyroidism, B12)
E: Eyes and ears (sensory isolation)
N: Normal Pressure Hydrocephalus (ataxia, incontinence, and dementia)
T: Tumor or other space-occupying lesion
I: Infection (syphilis, chronic infections)
A: Atrial fibrillation (vitamin B12 deficiency)/Alcoholism
S: Sleep Apnea

~10% of all Dementias
## DELIRIUM VS. DEMENTIA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Delirium</th>
<th>Dementia</th>
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</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Course</td>
<td>Fluctuating</td>
<td>Stable</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Attention</td>
<td>Fluctuates</td>
<td>Normal</td>
</tr>
<tr>
<td>Perception</td>
<td>Hallucinations</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Sleep/wake</td>
<td>Disrupted</td>
<td>Fragmented</td>
</tr>
<tr>
<td>Reversible</td>
<td>Usually</td>
<td>NOT reversible</td>
</tr>
</tbody>
</table>
COMMON DEMENTIAS IN OLDER PERSONS

- Hippocampal sclerosis of aging
- Primary age-related tauopathy (PART)
- Vascular dementia
- Lewy body dementia
  - Other Parkinsonian dementias
- Dementia of Diabetes
- Alzheimer’s disease
PRIMARY AGE RELATED TAUOPATHY
Hachinski score

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2</td>
</tr>
<tr>
<td>Clinical evidence of atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2</td>
</tr>
</tbody>
</table>

A total score of 4 or less is suggestive of a degenerative cause of dementia such as Alzheimer's disease.

A score of 7 or more is suggestive of vascular dementia.

from Hachinski et al, Arch Neurol 32; 1975: 632
Lewy-Body Dementia

**Onset:** Insidious.

**Progression:** Progressive and more rapid.

**Clinical features:**
- Interferes early with social functions.
- Memory impairment may be late.
- Prominent attention and visuospatial defects.
- Fluctuating levels of alertness.
- Recurrent visual hallucinations.
- Parkinsonism.
- Repeated falls.
- Systemized delusions.
- Syncope.

**Neuroimaging:** Lack of dopamine receptor uptake on SPECT.
BOTH HYPER AND HYPOGLYCEMIA IN DIABETES IS ASSOCIATED WITH DEMENTIA

- Diabetes increased odds of brain infarcts (odds ratio [OR] = 1.57, P < .0001), specifically lacunes (OR = 1.71, P < .0001), but NOT Alzheimer's disease neuropath

- Alzheimers Dement. 2016
  Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology.

  Abner EL

Individuals with diabetes were less likely to have β-amyloid (hazard ratio [HR] [95% confidence interval (CI)] was 0.48 [0.23–0.98]) and tangles (HR [95% CI] 0.72 [0.39–1.33]) but more likely to have cerebral infarcts (HR [95% CI] 1.88 [1.06–3.34])

Diabetes is related to cerebral infarction but not to AD pathology in older persons

Z. Arvanitakis, MD

Diabetes (present in 15% subjects) was associated with an increased odds of infarction (OR = 2.47, 95% CI: 1.16, 5.24). Diabetes was not related to global AD pathology score, or to specific measures of neuritic plaques, diffuse plaques or tangles, or to amyloid burden or tangle density
Alzheimer’s Disease

Hyperamyloidosis
AMYLOID CASCADE HYPOTHESIS

George and Joy Glenner
AD is an amyloidosis; 1984
Down’s Syndrome

John Hardy
1992

Dennis Selkoe

Alzheimer’s disease: Amyloid cascade hypothesis

Amyloid precursor protein
Neurons
Neurofibrillary Tangles
Neuronal loss
Gliosis
Diffuse plaque
Neurotic plaque
WHAT IS THE PHYSIOLOGICAL ROLE OF AMYLOID BETA PROTEIN?
NORMAL OLDER PERSONS HAVE AMYLOID-BETA PLAQUES

- Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques.
- Postmortem examination was performed on 137 residents (average age 85.5 years) of a skilled nursing facility whose mental status, memory, and functional status had been evaluated during life.
- Ten subjects whose functional and cognitive performance was in the upper quintile of the nursing home residents, as good as or better than the performance of the upper quintile of residents without brain pathology (control subjects), showed the pathological features of mild Alzheimer's disease, with many neocortical plaques. Plaque counts were 80% of those of demented patients with Alzheimer's disease.
- The unexpected findings in these subjects were higher brain weights and greater number of neurons (greater than 90 micron in a cross-sectional area in cerebral cortex) as compared to age-matched nursing home control subjects.
LOW DOSES OF AMYLOID BETA PROTEIN ENHANCE MEMORY

Figure 5. Low doses of Aβ 1-42 administered ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.

Figure 4. Low doses of Aβ 12-28 administered ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.
Low dose Beta-Amyloid enhances acetylcholine release from hippocampus
INHIBITION OF AMYLOID BETA PROTEIN INHIBITS LEARNING IN YOUNG ANIMALS

The physiological role of beta-amyloid is memory enhancement.
CYTOKINES IMPAIR COGNITION

Infused IL-1α (human)
Brain IL-1α (human)
Brain IL-1α (murine)
IL-1α Blocking Ab (human)
IL-1α Blocking Ab (murine)
Relay Mechanisms: Vagal, PGE-CVO, Endothelium, Inflame Cell

Mean Trials to Criterion

- human-1 alpha-Memory

NS/GS, h1α/GS, h1α/Ab/h1α

IV/PDS
DECREASED MEMORY

AMYLOID PLAQUES

AMYLOID Oligomer (soluble)

Presenilins/ApoE4

Mitochondria

DNA Mutants

OXIDATIVE DAMAGE

APOPTOSIS

NEUROFIBRILLARY TANGLES

BAPtist THEORY
Amyloid Beta and Memory

(APP = Amyloid Precursor Protein; BBB = Blood Brain Barrier)

**Genes**
- Early onset hyperamyloidosis
  - Type I
    - (Presinilin 1 and 2; APP)
- Late Onset Hyperamyloidosis
  - Type II
    - (ApoE4 and 33 other genes)

**Inflammation** (Cytokines)
- Vascular damage
- Infections
- Traumatic Brain Injury

**APP**

- Physiological
  - Increase Acetylcholine
  - Increase Memory

- Pathological Increase
  - Plaques without Memory Impairment
    - Impaired Cognition
      - ↑GSKβ
      - Tau phosphorylation
      - Neurofibrillary Tangles
  - Plaques with Memory Impairment
    - Brain Oxidative Damage
    - Damaged BBB
PICK’S DISEASE
FRONTO-TEMPORAL DEMENTIA
The Multiple Causes of Dementia
(CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

- Antiphospholipid Syndrome
- Atrial Fibrillation
- Hypertension
- Vascular Damage
- CADASIL Syndrome
- Infections
- Traumatic Brain Injury
- Multiple Sclerosis
- Systemic Lupus Erythematosus

Inflammation

- Blood Brain Barrier Damage
- Primary Age-related Tauopathy
- Hippocampal Sclerosis of Aging (TDP-43)
- Diabetes Related Dementia
- Lewy-Body Dementia

Cytokines

Dementia

Alzheimer-Fischer Disease
Hyperbetaamyloidosis
Type I (Young Onset)
Type II (Old Onset)

Treatable Causes
- Sleep Apnea
- Normal Pressure Hydrocephalus
- Vitamin B-12 Deficiency
- Vision and Hearing Defects
- Anticholinergic Drugs

Other Dementias
- Creutzfeld-Jakob
- Frontotemporal Dementias
- Progressive Supranuclear Palsy
- Corticobasal Dementia
- Fragile X Syndrome
- Korsakoff’s Syndrome
- MELAS Syndrome
- Parkinson’s Dementia
- Huntington’s Disease
- Lyme’s Disease
- Progressive Nonfluent Aphasia
MANAGEMENT OF COGNITIVE DYSFUNCTION

Exclude Treatable Causes
- Anticholinergic drugs
- Depression
- Hypothyroid (TSH)
- Vitamin B12 deficiency
- Hearing and visual problems
- Atrial fibrillation
- Sleep Apnea

Lifestyle
- Mediterranean diet
- Olive oil
- Exercise
- Computer games
- Socialization
- Cognition Stimulation Therapy
- Refer to Alzheimer’s Association
- Safe return bracelet
- Discuss driving/guns

MEDS?
Results 22 trials met the inclusion criteria. Follow-up ranged from six weeks to three years. 12 of 14 studies measuring the cognitive outcome by means of the 70 point Alzheimer's disease assessment scale—cognitive subscale showed differences ranging from 1.5 points to 3.9 points in favour of the respective cholinesterase inhibitors. Benefits were also reported from all 12 trials that used the clinician's interview based impression of change scale with input from caregivers (0.26-0.54). Methodological assessment of all studies found considerable flaws—for example, multiple testing without correction for multiplicity or exclusion of patients after randomisation.
257 were included in the systematic review.

In pooled trial data, cholinesterase inhibitors (ChEIs) produce small improvements in cognitive, functional, and global benefits in patients with mild to moderate Alzheimer's and Lewy body dementia, but the clinical significance of these effects are unclear.

The efficacy of ChEI treatment appears to wane over time, with minimal benefit seen after 1 year.

There is no evidence for benefit for those with advanced disease or those aged over 85 years.

Adverse effects are significantly increased with ChEIs, in a dose-dependent manner. A two- to fivefold increased risk for gastrointestinal, neurological, and cardiovascular side effects is related to cholinergic stimulation, the most serious being weight loss, debility, and syncope.

Those aged over 85 years have double the risk of adverse events compared with younger patients.
MEMANTINE: N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST

TEAM-AD VA Cooperative Randomized Trial

<table>
<thead>
<tr>
<th>ADCS-ADL Inventory</th>
<th>Vitamin E (n = 140)</th>
<th>Memantine (n = 142)</th>
<th>Vitamin E + Memantine (n = 139)</th>
<th>Placebo (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score, mean (SD)</td>
<td>57.20 (14.38)</td>
<td>57.77 (13.78)</td>
<td>57.16 (13.59)</td>
<td>56.93 (13.61)</td>
</tr>
<tr>
<td>Least squares mean (SE) change from baseline</td>
<td>-13.81 (1.11)</td>
<td>-14.98 (1.10)</td>
<td>-15.20 (1.11)</td>
<td>-16.96 (1.11)</td>
</tr>
<tr>
<td>Mean change difference compared with placebo (95% CI)</td>
<td>3.15 (0.92 to 5.39)</td>
<td>1.98 (-0.24 to 4.20)</td>
<td>1.76 (-0.48 to 4.00)</td>
<td></td>
</tr>
</tbody>
</table>

Post-hoc analysis of trials suggested a potential effect on agitation and aggression in AD.

Major adverse effects: orthostatic hypotension and falls

EXERCISE AND THE BRAIN

- Aerobic exercise for 6 months...

Decreased brain atrophy

Increased cognition

Decreased dysphoria

LIFE Study suggests need for high dose exercise

Colcombe et al
J Gerontol A 2006; 61:1166
A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

FINGER STUDY

Aged 60-77 years recruited from previous national surveys. A 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). 1260 to the intervention group (n=631) or control group (n=629).
Improves Cognition
CONCLUSION

- Early diagnosis and interventions are important
- Use a validated instrument to help diagnose (RCS)
- Identify and treat reversible causes
- Name the specific dementia type using clinical history, exam findings +/- brain imaging
- Treatment should not begin until a diagnosis has been established and should include
  - Lifestyle interventions (EXERCISE!)
  - Cognitive stimulation
  - Social support services
  - Advance care planning
  - Consideration for medication management with goal to reduce polypharmacy
Questions?