OVERVIEW OF DEMENTIA

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COMING TO TERMS WITH AD

• What is it?
• Why is it important?
• How to differentiate it?
• How to understand it?
• How to deal with it effectively?
• Why the need for further research?
INTRODUCTION

• In general geriatric psychiatry, the majority of patients will be diagnosed with one of the 3 D’s: Delirium, Depression and Dementia.

• Those diagnosed with one d/o are at risk for developing a second of the 3 D’s; Demented patients have a 10-20 time > incidence of developing depression than community elders.

• Considerable overlap in the diagnostic criteria of these d/o’s.
DEMENTIA DEFINITION (DSM-IV)

- Multiple Cognitive Deficits including:
  - 1) Memory Dysfunction (especially new learning)
  - 2) at least one additional cognitive deficit; aphasia, apraxia, agnosia or executive function
- Cognitive disturbances must be sufficiently severe to cause impairment of occupational or social functioning and must present a decline from previous level of functioning
DEMENTIA DIAGNOSIS (DSM-V)

• Major/Mild Neurocognitive Disorder (NCD)
  • Evidence of a moderate or significant cognitive decline from previous performance in 1 or more cognitive domains: complex attention, executive functioning, learning and memory, language, or social cognition
  • Modest to severe Impairment documented in cognitive performance preferably by neuropsychological testing
DIFFERENTIAL DIAGNOSIS
MILD VS MAJOR

• IADLs
  • The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.)
TYPES OF MAJOR/MILD NCD

- Alzheimers Disease
- Vascular Dementia
- Lewy Body Disease
- Parkinson’s Disease
- TBI
- Frontal Temporal Lobar Degeneration (FTLD)
  - Behavioral Variant
  - Primary Progressive Aphasia
  - Pick’s Disease
  - Corticobasal Degeneration
  - Progressive Supranuclear Palsy
TYPES OF DEMENTIA
(HISTORY)

• Alzheimer’s Dementia
  • Putative Risk Factors
    • AGE (Greatest Risk)
    • Family History
    • Head Trauma
    • Low Educational level
    • Family History of Down’s Syndrome
    • Possibly late onset depression

• Course and History
  • Insidious Onset (usually after the age of 65)
  • More common in women
  • Cognitive Impairment noticed first
  • Gradual and Progressive (behavioral changes and psychosis)
WHY WOMEN MAY HAVE INCREASE RISK?

- Women Live Longer (Age greatest Risk Factor)
- Potentially due to biological or genetic variations or different life experiences (type and amount of education, or occupational choices)
- Men who make it pass age 65 maybe more cardiovascularly healthy than females
- Interaction of APOE-e4 and estrogen
ALZHEIMER’S DISEASE (AD): MORE THAN JUST MEMORY LOSS

• AD is a progressive, degenerative disease involving:
  • Loss of memory and other cognitive functions
  • Decline in ability to perform activities of daily living
  • Changes in personality and behavior
  • Increases in resource utilization
  • Eventual nursing home placement
ALZHEIMER’S WARNING SIGNS - TOP TEN

• 1) Recent memory loss affecting job
• 2) Difficulty performing familiar tasks
• 3) Problems with language
• 4) Disorientation to time and place
• 5) Poor or decreased judgement
• 6) Problems with abstract thinking
• 7) Misplacing things
• 8) Changes in mood or behavior
• 9) Changes in personality
• 10) Loss of initiative
EARLY CLINICAL SIGNS OF AD

- Asking the same question over and over again
- Repeating the same story, word for word, again and again
- Forgetting how to perform common tasks previously performed with ease, such as cooking, making repairs, playing cards
- Losing one’s ability to pay bills or balance one’s checkbook
- Getting lost in familiar surroundings, or misplacing household objects
- Neglecting to bathe, wearing the same clothes over and over again, while insisting they have taken a bath or that their clothes are still clean
- Relying on somebody else, such as a spouse, to make decisions or answer questions

PROGRESSION OF ALZHEIMER’S DEMENTIA

Mild
- Short-term memory loss
- Word-Finding Trouble
- Mood Changes

Moderate
- Behavioral, personality changes
- Long-term memory affected
- Wandering, agitation, aggression, confusion
- Require assistance with ADLs

Severe
- Increase in behavioral disturbances
- Loss of ADL capacity
- Incontinence
- Motor disturbances
- Placement in long-term care facilities
THE PROGRESS OF ALZHEIMER'S DISEASE

Years

MMSE score

Early Diagnosis

Cognitive Symptoms

Mild-Moderate

Severe

Loss of ADLs

Behavioral Problems

Nursing Home Placement

Death

TYPES OF DEMENTIA (HISTORY)

• Vascular Dementia
  • Putative Risk Factors
    • Vascular Insult (White Matter Ischemic Changes, lacunar infarcts, chronic small vessel ischemic disease)
    • Hypercholesterimia, hyperlipidemia, and hypertension

• Course and History
  • Insidious
  • Step-wise deterioration
  • Waxing and Waning
  • Behavioral and Cognitive Symptoms noticed first. Not unusual for Behavioral symptoms first
VASCULAR DEMENTIA

• Cerebrovascular Disease: Focal Neurologic signs, Evidence on brain imaging (Multiple large vessel infarcts or Single strategically placed infarct)

• Onset of Dementia within 3 months following a stroke or Abrupt deterioration of functioning or Fluctuating stepwise progression
TYPES OF DEMENTIA (HISTORY)

• Fronto-temporal lobe dementia (FTD)
  • Risk Factor
    • Family History of a similar dementia
    • Thyroid disease
    • Head Trauma
  • Course
    • Mean age is 52
    • More Common in Men
    • Significant Behavior and Personality Changes then Cognitive Impairment
TYPES OF DEMENTIA (HISTORY) CONT...

- Dementia due to Lewy Body Disease
  - Progressive Cognitive Decline
  - At least two of the following
    - Parkinsonism or gait imbalance
    - Visual Hallucinations
    - Visuospatial Impairments
    - Waxing and Waning Cognitive Ability
PREVALENCE OF ALZHEIMER’S DISEASE

PREVALENCE OF AD

• Currently, 5.3 million Americans suffer from AD (5.1 million >65 yo and 200,000 under 65 y.o.)

• 81% of individuals who suffer from AD are 75 years or older

• Older African Americans and Hispanics are more likely than older whites to have Alzheimer’s
  • Possibly due to variations in health, lifestyle, and socioeconomic risk factors.
MONETARY COSTS OF DEMENTIA IN THE U.S.

• The estimated prevalence of dementia among persons older than 70 years of age in the United States in 2010 was 14.7%.

• The yearly monetary cost per person that was attributable to dementia was either $41,689-$56,290.

• These individual costs suggest that the total monetary cost of dementia in 2010 was between $157 billion and $215 billion.

RAND Study, NEJM 2013, M. Hurd
DIFFERENTIALS

• Depression (Pseudodementia)
• Delirium
  • Drugs
  • Metaboloic/Endocrine Changes
  • Infections (UTI)
  • Traumas
  • NPH
  • Alcohol
DEPRESSION

- Onset = Rapid
- Precipitants = Psychosocial
- Duration = Less than 3 months to presentation
- Mood = Depressed, anxious
- Behavior = Decreased activity or agitation
- Cognition = Unimpaired or poor responses
- Somatic Symptoms = fatigue, lethargy, sleep, appetite
- Course = Rapid resolution with treatment, but may precede Alzheimer’s
DRUGS

• Anticholinergics: Benztropine, amitryptaline, scopolamine, hyosciamine, oxybutinlin, diphenhydramine
• GABA Agonists: Benzodiazepines, barbiturates, ethanol, anti-convulsants
• Beta blockers: Propranolol
• Dopaminergics: L-dopa, alpha-methyl-dopa
MEDICAL/ENDOCRINE

- Thyroid Dysfunction (Hyper or Hypo)
- Diabetes
- Hypoglycemia
- Hypercalcemia
- Nephropathy, Uremia
- Hepatic Dysfunction (Wilson’s Disease)
- Vitamin Deficiency (B12, Thiamine, Niacin)
TRAUMA

• Concussion, contusion
• Subdural hematoma
• Hydrocephalus; normal pressure (late effect of bleed)
• Possible contributor to Alzheimer’s Dementia initiation
INFECTIOUS CONDITIONS

• HIV
• Neurosyphilis
• Viral Encephalitis (Herpes)
• Bacterial Meningitis
• Fungal Infection (Cryptococcus)
• Prion (Jakob-Creutzfeldt Disease)
CAN’T BE DONE WITHOUT THESE

- History
- Testing and Imaging
- Clinical Observation
LABORATORY TESTS

• Blood Tests: Electrolytes, LFT’s, Kidney function tests, glucose, Thyroid function tests, B12, folate, CBC, VDRL, HIV (if indicated)
• EKG
• CXR
• UA
• NEUROIMAGING
NEUROPSYCHOLOGICAL TESTING

- Memory; short term and remote
- Verbal function; Fluency
- Visuo-spatial function
- Attention
- Executive function
- Abstract thinking
- Account for education and social function
SEVERITY ASSESSMENT

• MMSE / MOCA

• Verbal Fluency

• Full Neuropsychological Evaluation

• IADL Measures
As AD progresses, loss of function becomes more evident.

VISUOSPATIAL ASSESSMENT

- Clock Drawing
BEHAVIORAL PROBLEMS

- Mood disorders
- Psychotic disorders
- Inappropriate behaviors
- Aggression: verbal, physical
- Purposeless activity: verbal, motor
- Meal time behaviors
- Sleep disorders
HALLMARKS OF ALZHEIMER’S

• Nerve cell loss
• Beta Amyloid Plaques (with amyloid cores) – Occur outside the neurons
  • Interfere with the neuron to neuron communication
• Neurofibrillary tangles (abnormally phosphorylated tau proteins) – Occur within the neurons.
  • Blocks the transport of nutrients and other essential molecules inside neurons
AP = amyloid plaques
NFT = neurofibrillary tangles

Courtesy of George Grossberg, St Louis University, USA
GENETICS DO PLAY A ROLE

• 1% or Less of Alzheimer’s
  • Mutation of the Amyloid Precursor Protein (APP), Presenilin 1 and Presenilin 2
    • Positive for mutation of APP or Presenilin 1 gene guaranteed to develop Alzheimer’s Disease
    • Positive for Presenilin 2 gene have a 95% chance of developing the disease
    • Presence of any of these 3 genes develop Alzheimer’s symptoms prior to the age of 65.
• Apolipoprotein E Gene
  • Provides the blueprint for a protein that transports cholesterol in the bloodstream. You have 1 of 3 variants (e2, e3 or e4)
    • e2 decreases the risk of developing AD
    • One copy of e4 increases the risk of AD by 3 folds and 2 copies of e4 8 to 12 fold higher risk
      • Initial stages occur younger
      • 40-65% of AD Patients have 1 or 2 copies of e4

Treatment benefits were lost when donepezil was discontinued as measured by the decline in ADAS-cog scores in an open-label extension of Study 302.

*Other studies have estimated the decline to range from 6 to 12 points annually.

LONG-TERM COGNITIVE BENEFITS OF GALANTAMINE TREATMENT


* P<0.05 vs. placebo/galantamine (not statistically different from baseline)
A 24-week, placebo-controlled, clinical trial of donepezil in patients with moderate to severe AD (MSAD)

Objective:
- Evaluate the safety and efficacy of donepezil in patients with moderate to severe AD (sMMSE: 5-17)
- Efficacy data shown within this presentation are for the subset of patients with baseline sMMSE scores of 10-17

Design:
- 24-week, multicenter, randomized, double-blind, placebo-controlled study
- 201 patients within the 10-17 cohort were randomized to:
  - Donepezil (n=97)
  - Placebo (n=104)
- Donepezil-treated patients received 5 mg/day for 28 days. At Week 4 the dose could be increased to 10 mg/day based on clinician’s judgment
  - 70% of patients in the sMMSE 10-17 cohort received 10 mg/day for the duration of the study
- Patients were evaluated at baseline and Weeks 4, 8, 12, 18, and 24

Data on file. Eisai Inc., Teaneck, NJ.
NPI scores favored donepezil on all behavioral domains

Data shown are for the moderate cohort of MSAD only (sMMSE: 10–17)

*P<0.05 vs placebo

Holmes Study (MMSE 10-27)

Aricept showed significant efficacy in treating behavioral symptoms in mild-to-moderate AD.

N = 128.
*P<0.0001; †P<0.005.
MEMANTINE COMBINATION THERAPY WITH DONEPEZIL

**Design**
- A US multicenter, randomized, double-blind, placebo-controlled trial

**Population**
- 404 subjects with moderate-to-severe AD (MMSE range, 5-14) receiving donepezil at least 6 months (3 months, stable dose)

**Treatment**
- Memantine 20 mg/day (10 mg BID) or placebo
- All subjects received donepezil (ChE-I) for study duration

**Duration**
- 24 weeks

COGNITION: SEVERE IMPAIRMENT BATTERY (SIB)

Mean Change from Baseline (± SEM)

-4 -3 -2 -1 0 1 2 3 4

Treatment Week

0 4 8 12 18 24

Memantine/Donepezil

Placebo/Donepezil

*P< 0.05

**P< 0.001

Least square mean change, ANCOVA

ITT population, LOCF

FUNCTION: ACTIVITIES OF DAILY LIVING (ADCS-ADLSEV)

Mean Change from Baseline (± SEM)

-0.5 -1 -1.5 -2 -2.5 -3 -3.5 -4

0 4 8 12 18 24

Treatment Week

Memantine/Donepezil
Placebo/Donepezil

* P < 0.05

Least square mean change, ANCOVA ITT population, LOCF
DEMENTIA SYNDROME

- Behavioral Manifestations: Apathy, Agitation, Irritability, Anxiety, Disinhibition, Motor Dysregulation (wandering, pacing), Depression, Appetite Changes, Delusions, Night Behaviors (Sundowning), Hallucinations, Euphoria, Incontinence
TREATING THE DEMENTIA SYNDROME

- Unfortunately, few controlled studies of psychotropic agents in dementia
- No medication currently approved by the U.S. FDA for the treatment of Bx disturbance in dementia
- Currently used Medications: Antipsychotics, Benzodiazepines, Buspirone, Beta-blockers CBZ, Li, SSRIs, Divalproex
FUTURE DIRECTION?

• Eli Lilly and Company - semagacestat, a gamma secretase inhibitor being studied as a potential treatment for Alzheimer's disease. Plaque Buster?? Worsened cognition greater than placebo
SUMMARY

• Dementia diagnosing is increasing in frequency
• Treatments to offset the natural progression of the illness are needed yet not currently available
• With illness progression appropriate pharmacological interventions are necessary
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