Dementia Update

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Nothing to disclose
Dementia

• Progressive deterioration in mental function including;
  – Cognition (learning, memory, attention),
  – language,
  – social skills
  – Personality and behavior
  – Executive functions
  – Visual perceptual functions (vision)
Classification

- Degenerative
  - Alzheimer’s Disease
  - Lewy Body Disease
  - Frontoemporal Dementia

- Non-Degenerative
  - Vascular
  - Paraneoplastic
  - Autoimmune
  - Inflammatory
  - Prion Disorders (CJD)
Alzheimer’s Disease

• In 2015, 5.3 million American had Alzheimer’s Disease (AD)
• 5.1 million are over the age of 65 and 200000 less than age 65
• Two thirds of persons with AD are women
• Older African-American and Hispanics more likely to have AD.
• By 2025 the number of people with AD in the United States expected to rise to 7.5 million (40% increase) and to 13.8 million by 2050
Risk Factors

• **Age**
• (Mild Cognitive Impairment)
• Family history
• Genetics
  – Apoe-e4 allele
  – Presenile 1 (PS1)
  – Presenile 2 (PS2)
  – Amyloid Precusor Protein (APP)
• Traumatic Brain Injury
• Hypertension, hypercholesterolemia, diabetes, stroke, heart disease
Four Presentation Variants of AD

• Amnestic (Main deficit is memory)
• Visual (Main deficit is vision, Posterior Cortical Atrophy)
• Aphasic (Main deficit is language)
• Behavioral (Main deficit is behavioral changes)

• Each presentation is associated with a specific pattern of amyloid and tau deposition
BvAD

Logopenic dementia (LaAD)

Amnestic AD

PCA
Cognitive Continuum

Normal

Mild Cognitive Impairment

Alzheimer’s Disease
Successful aging

Typical aging

Function

Time

MCI

Dementia
Mild Cognitive Impairment

MCI $\rightarrow$ AD 12%/yr

Control $\rightarrow$ AD 1-2%/yr
Diagnosis of Alzheimer’s Disease

- History
- Neurological Exam
- Neuropsychological Testing (can quantify and characterize cognitive domains affected)
- Neuroimaging
  - Structural; CT and MRI
  - Functional; SPECT and PET
  - Amyloid Imaging;
- CSF markers
Alzheimer’s Disease Amyloid Scan
CSF Markers of Alzheimer’s Disease

Interpretation
This individual possesses cerebrospinal levels of Aβ1-42 peptide, total tau and phospho-tau protein which are consistent with a diagnosis of Alzheimer’s (AD) disease as a cause of his/her neurological symptoms.1-11

Technical Results
Aβ42  482.5 pg/ml
T-Tau  1030.5 pg/ml
P-Tau  136.9 pg/ml
ATI    0.33

Patient data is plotted on the graph below to illustrate the relative position of this individual’s result compared to recognized reference points for diagnostic cutoff values (AT Index of 1.0 and P-tau concentration of 61 pg/ml). Clinical studies indicate that ranges for all three biomarkers overlap to some extent (zones of 0.8 to 1.2 AT index and 54 - 68 pg/ml P-tau shown on the graph) between the AD and non-AD populations as reflected in the sensitivity and specificity figures.
Treatment of Alzheimer’s Disease

• Only two FDA approved meds
  – Cholinesterase Inhibitors
    • Donepezil, Rivastigmine, Galantamine
    • Inhibits the enzyme acetylcholinesterase from breaking down acetylcholine, increasing the level and duration of action of the neurotransmitter acetylcholine
  – Provides a window of symptomatic improvement
  – Do not slow down the rate of progression
  – Seem to “lose effect” after a few years
  – Memantine; May be helpful in patients with severe Alzheimer’s Disease
Lewy Body Disease

• The terms “Dementia with Lewy Body (DLB)” and “Lewy Body Dementia (LBD)” often used interchangeable.

• Second most frequent cause of dementia
  – Incidence 3.5 per 100K, prevalence 1.3 million

• Neuropathology closely related to Parkinson’s Disease (alpha synuclein deposition)
LBD Symptoms (Criteria)

• Central Feature
  – Dementia (different from Alzheimer’s Disease)

• Core Features
  – Fluctuating cognition
  – Complex visual hallucinations
  – Parkinsonism (rigidity, bradikiniesia, etc)

• Suggestive Features
  – REM Behavior Disorder
  – Hypersensitivity to Neuroleptics
  – Low dopamine transporter uptake in the basal ganglia (DAT SPECT)
Supportive Features

- Repeated falls and syncope (fainting).
- Transient, unexplained loss of consciousness.
- Autonomic dysfunction.
- Hallucinations of other senses, like touch or hearing.
- Visuospatial abnormalities.
- Other psychiatric disturbances.
REM sleep behavior disorder

- A parasomnia featuring:
  - Violent dreaming, often described as being chased or attacked by people or animals
  - Leads to violent physical activities during sleep
    - Thrashing about in sleep
    - Falling out of bed
    - Striking bed partner
    - Physical injuries
- A powerful predictor of subsequent DLB (or multiple system atrophy), up to 10 years later
70 year old male severe RBD
LBD
DATScan (high affinity for dopamine transporters)
Interwoven therapy of DLB

- Cognition: cholinesterase inhibitor, levodopa, antipsychotic
- Movement disorder: levodopa, clonazepam, antidepressant
- Visual Hallucinations: anticholinergics
- Sleep disorder: clonazepam, antidepressant
- Depression: antidepressant
- Orthostatic hypotension: midodrine
- incontinence: anticholinergics
- Excessive daytime sleepiness: ?
Fronto-temporal Dementia

- Third most frequent cause of dementia
- Three variants, each with relatively specific brain localization (as per MRI and PET)
  - Behavioral
  - Language (Aphasia)
  - Semantic Dementia (loss of word meaning)
- Three mutations have been associated with FTD
  - Progranulin on Chromosome 17
  - C9orf72 on Chromosome 9
  - Microtubule Associated Protein tau on Chromosome 17
  - VCP
- Three proteins
  - Phosphorylated Tau
  - TAR-DNA-binding protein 43 (TDP-43)
  - Fused in sarcoma (FUS) protein
Clinical syndrome by protein

Clinical diagnosis

- bvFTD (n=128)
- FTD-MND (n=32)
- agPPA (n=27)
- SD (n=18)
- PSPS (n=35)
- CBS (n=34)

Percentage

FTLD-tau
FTLD-TDP
The FTD spectrum has been linked to genetic causes.
Behavioral variant of FTD

• Most common clinical syndrome associated with FTLD
• Characterized by changes in behavior & personality & executive dysfunction
• Can be familial
• Can be associated with MND
• Variable degrees of R & L frontotemporal atrophy & hypometabolism

Social Cognition and BvFTD
Theory of Mind

• Understand and predict how another person thinks, feels and behaves when faced with a particular situation

• Empathy: perhaps one of the most magnificent of human abilities

• Deceit: putting ourselves in the “mind of our enemies” so as to prepare an ambush
Neurobiology of TOM

• There is a well defined brain system that becomes active with TOM functions
• There are some areas of the brain which seem to be highly dedicated to TOM functions
• BvFTD can affect TOM very early in its course.
Progressive non-fluent aphasia

- Speech output is hesitant and non-fluent
- Some cases familial
- Typically associated with atrophy of the left perisylvian region
- However, non-fluency was not more specifically defined and could have been secondary to word finding difficulties resulting in pauses, or to speech production impairment (apraxia of speech, AOS)
Semantic dementia

• Multimodal disorder with aphasia and agnosia
• Loss of “word meaning”
• Not familial
• Not associated with MND
• When aphasia is the dominant feature it is referred to as the semantic variant of PPA
  – Left anterior medial temporal lobe atrophy
• Right temporal variant is usually misdiagnosed as bvFTD

Frontotemporal dementia with motor neuron disease (FTD-MND)

- Combines features of FTD (behavioral dyscontrol, executive dysfunction, agrammatic aphasia) with features of lower motor neuron disease
- Cognitive and behavioral symptoms predate motor symptoms
- If motor symptoms predate the cognitive symptoms, we use the term ALS-dementia

Mitsuyama. J Neurol Neurosurg Psychiatry. 1984
Summary

• The neurodegenerative dementias include AD, LBD and FTD
• Each has a specific clinical and pathological spectrum
• Definitive diagnosis can only be made with neuropathological analysis
• Functional and structural findings as well as biomarkers can “narrow” the diagnosis
Dementia with Lewy Bodies

Case 1

Case 2