Pathophysiology of dementia

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Outline:

• Definition of dementia
• Types of dementia
• Pathophysiology of dementia--focus on Alzheimer’s disease
DEMENTIA DEFINITION

• “Acquired losses of cognitive and emotional abilities severe enough to interfere with daily functioning and quality of life” (NEJM review)
Diagnostic assessment of dementia

- History is the most important aspect (nature of onset, rate of progression, evidence of functional impairment, “neuropsychiatric symptoms”)
- Examination includes mental status exam - MMSE, etc.
- Laboratory assessment should focus on exclusion of treatable diagnoses (TSH, vitamin B12 level, brain imaging)
- Dementia diagnosis is a clinical exercise - PET scans, genetic tests, etc are imperfect
Common causes of dementia

- Alzheimer’s disease
- Vascular dementia (multiple strokes)
- Lewy body dementia
- Frontotemporal dementia
What does diagnosis have to do with pharmacotherapy?

- Drug trials may be contaminated by other diagnoses
- Clinical diagnosis of AD is confirmed at autopsy in 90% of cases
- Co-incidence of cerebrovascular and Alzheimer pathology is very common
- Co-incidence of Alzheimer and Lewy Body pathology is also common
Vascular dementia-diagnostic criteria:

- 1907: Alzheimer’s describes a dementia in middle aged woman
- 1970: Tomlinson, Blessed and Roth make the case that senile dementia is also Alzheimer’s plaque and tangle disease
- 1992: California criteria
- 1993: NINDS-AIREN criteria
- 1993: WHO criteria
- 1994: DSM-IV
Research community: clinical practice discrepancy

• Vascular dementia is common in the community
  – (because the coincidence of vascular disease and dementia is common)

• Vascular dementia is rare in an Alzheimer’s center
  – (Because the diagnostic criteria are fairly stringent)
Vascular dementia-summary

- Diagnostic criteria vary widely
- Vascular and Alzheimer pathology often co-exist, *and probably interact* to result in dementia syndrome
Dementia with Lewy bodies

- Pathologic diagnosis
- Clinical criteria = Dementia, plus:
  - Parkinsonism
  - Neuroleptic sensitivity
  - Visual hallucinations
  - Fluctuations
- These criteria are not very sensitive or specific
Dementia with Lewy bodies - neurotransmitters

- Path studies show marked cholinergic deficit
- Lewy body patients often dramatic responders to CEI’s
- Interestingly, hallucinations often respond to CEI’s
Dementia with Lewy bodies

- Clinical criteria are not very sensitive
- Co-occurrence of Lewy bodies with AD pathology is common
- Cholinergic deficit may be even more severe than in “pure” AD
- Diagnostic challenges inhibit clinical trials, but this is an area of active research
Frontotemporal dementia

• Prominent personality change (eg, disinhibition, bizarre behavior, apathy, withdrawal) preceding memory dysfunction
• Pick’s disease is one type
• Current practice is to lump a number of histologies and clinical syndromes into this category
Frontotemporal dementia - pathology

- Disproportionate frontal and temporal atrophy
- Pick bodies (Pick disease)
- Neuronal achromasia (Corticobasal degeneration)
- DLDH
Frontotemporal dementia - neurotransmitters

- No path evidence of a cholinergic deficit
- Serotoninergic deficit?
Biology of non-Alzheimer dementias: conclusions

- Vascular dementia, Dementia with Lewy Bodies: common co-morbidity with plaques and tangles.
- FTD: a mixed bag of relatively rare diseases, including at least one tauopathy
Alzheimer’s disease

• Clinical presentation, natural history
• Brain pathology
• Pathophysiology:
  – Amyloid, inflammation, oxidative stress, excitotoxicity, estrogen, cholesterol, aging
ALZHEIMER’S DISEASE: WHAT HAPPENS TO THE PATIENT?

• Memory is usually affected first, in a slowly progressive fashion

• Language skills and visuospatial skills are then often affected

• “Activities of Daily Living” also slowly decline
ALZHEIMER’S DISEASE: WHAT HAPPENS TO THE PATIENT?

- Psychiatric symptoms also emerge, though the nature of these symptoms is especially varied
- Some become depressed and apathetic
- Some become delusional and paranoid
- Some become anxious and restless
ALZHEIMER’S DISEASE:
WHAT HAPPENS TO THE PATIENT?

• Neurologic problems also frequently develop
• “Parkinsonism”, with rigidity, slow movements, and gait problems may appear
• Seizure disorders occasionally appear
AD HAS A LONG COURSE

• Mean is 8 - 10 years from diagnosis to death
• Mean is loss of about 3 points on MMSE/year
• “CDR” stages:
  » 0.5 “mild cognitive impairment”, “qdem”
  » 1.0 “mild dementia”
  » 2.0 “moderate”
  » 3.0 “severe”
SYMPTOMATOLOGY IN AD IS VARIED

• Cognitive impairment
• Functional impairment
• “Psychiatric” symptoms -- delusions, hallucinations, depression, anxiety
• Rate of decline
ALZHEIMER’S DISEASE: WHAT HAPPENS TO THE BRAIN?

- Abnormal proteins are laid down in “plaques,” and “tangles” appear within brain cells.
- Somehow this leads to brain cell dysfunction and eventually death.
- Neurotransmitters are also depleted—acetylcholine deficit correlates with severity.
CEREBRAL ATROPHY

Amyloid Precursor Protein

β-amyloid in solution

β-amyloid in plaques

Brain cells get sick

Brain cells wither & die

Inflammation
Oxidative Stress
Cholesterol

Estrogen Growth Factors

Brain chemicals are depleted (especially the neurotransmitter, acetylcholine)
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Neuron and Acetylcholine

Presynaptic nerve terminal

AChE inhibitor

Nicotinic receptor

Acetylcholinesterase (AChE)

Acetylcholine (ACh)

Muscarinic receptor

Acetic acid

Choline

Postsynaptic nerve terminal

In one controlled clinical trial of 30 weeks duration in 473 patients, 154 patients were randomly assigned to receive daily doses of 5 mg. One hundred fifty-seven patients were randomly assigned to receive daily doses of 10 mg. One hundred sixty-two patients were randomized to placebo. The 30-week trial was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period.
DONEPEZIL HCl (ARICEPT™) ADAS-cog PLACEBO WASHOUT EFFECT*

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Rivastigmine Effect on ADL:

PDS (Corey-Bloom)


* p < 0.05.

** p < 0.001.
CEI’s

• Why do they work?
  – Because a cholinergic deficit plays a role in Alzheimer’s symptomatology

• Why don’t they work better?
  – Because the cholinergic deficit is not the whole story (plaques, tangles, neuronal death)

• What other mechanisms may be treated?
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Excitotoxicity and AD

- Glutamate is an excitatory neurotransmitter
- Glutamate can be neurotoxic (established in stroke, seizure)
- Excitotoxicity is mediated by NMDA receptor
- But NMDA blockers often hallucinogenic
Excitotoxicity as a treatable mechanism in AD

- Excitotoxicity is mediated by the NMDA receptor, which mediates neurotoxic effects of glutamate
- Memantine is an NMDA receptor antagonist
- Theoretically neuroprotectant
- Memantine is a non-cholinergic drug (so no GI side effects)
Mean MMSE at baseline = 7.7

“Memantine in moderate to severe Alzheimer’s disease”
Reisberg et al, NEJM 2003; 348: 1333-1341
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Table 3. Most Frequently Reported Adverse Events.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Memantine (N=126)</th>
<th>Placebo (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>106 (84)</td>
<td>109 (87)</td>
</tr>
<tr>
<td>Agitation</td>
<td>23 (18)</td>
<td>40 (32)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>14 (11)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (6)</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (10)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (10)</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

* Adverse events occurring in at least 10 percent of the patients in either treatment group are reported.

“Memantine in moderate to severe Alzheimer’s disease”
Reisberg et al, NEJM 2003; 348: 1333-1341
Donepezil vs. donepezil + memantine

“Memantine treatment in patients with moderately severe Alzheimer’s disease already receiving donepezil”
Tariot et al, JAMA 2004; 291:317-324
Memantine in earlier phases of dementia:

• 2/3 trials in mild to moderate AD failed to show efficacy
• No data on efficacy in “pre-dementia” (MCI)
Unanswered questions re memantine:

• Why would a neuroprotectant be more effective later in the disease?
• Why do the data in the clinical trials look like a symptomatic, rather than a neuroprotectant therapy?
• Is memantine truly neuroprotectant, or another symptomatic therapy?
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Oxidative damage and Alzheimer’s
Oxidative damage and Alzheimer’s

Age spots on your skin signal that a brown slime is forming on the neurons of your brain!
Oxidative damage and AD

• Increased oxidative end-products in AD brain
• Beta amyloid neurotoxicity ameliorated by antioxidants in vivo
• Protection with antioxidant rich diets??
• Vitamin E study-proof of concept?
Vitamin E trial in Alzheimer’s disease:
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Evidence for inflammation:

- Increased levels of inflammatory mediators in AD brain and body fluids
- Inflammatory mediators localized to brain lesions
- Reduced incidence of AD in NSAID users
Clinical trials of anti-inflammatory agents for treatment of Alzheimer’s disease

- Prednisone vs placebo-failed
- Naproxen vs rofecoxib vs placebo-failed
- Plaquenil vs placebo-failed
Clinical trials of anti-inflammatory agents for prevention of Alzheimer’s disease

- Celebrex vs placebo in “MCI”-failed
- Naproxen vs celebrex vs placebo in subjects with family history--aborted due to excess morbidity in NSAID-treated subjects
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Estrogen-rationale

• Reduced incidence of dementia in women on estrogen replacement (since revised)
• Estrogen receptors in brain
• Neurotrophic effects of estrogen in animals
Clinical trials of estrogen in AD

- All failed:
  - Mulnard et al, JAMA 2000
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Cholesterol and AD

- Hypercholesterolemia is a risk factor for dementia
- High cholesterol diet accelerates plaque pathology in transgenic mice
- Cholesterol localized to plaque?
- Lower incidence of dementia in statin users
- Apo E carries cholesterol and modifies risk of AD
APOLIPOPROTEIN E

• Apolipoproteins are cholesterol-transporting proteins

• 3 ApoE alleles: E2, E3, E4

• about 50% of AD subjects have E4, 15% of normal population has E4

• Effect is dose-dependent: E4/E4 is highest risk

• A risk factor, not a causative gene
APOLIPOPROTEIN E: NOT A DIAGNOSTIC TEST

- 50% of patients with AD are E4 negative
- Only 25 - 40% of subjects with one E4 allele will develop AD
- Those with no E4 allele are still at risk for AD
- Even E4/E4 homozygotes are estimated to have only a 30% lifetime risk of developing AD
Cholesterol and AD

• NIH-sponsored placebo-controlled trial of statins recently completed: no evidence that statins slow the rate of progression of Alzheimer’s
Pathophysiology-theories

- Cholinergic deficit
- Excitotoxicity
- Oxidative damage
- Inflammation
- Estrogen
- Cholesterol (Apolipoprotein E?)
- Amyloid toxicity
Anti-amyloid strategies:

- Amyloid Precursor Protein
- β-amyloid in solution
- β-amyloid in plaques
- Brain cells get sick
- Brain cells wither & die
- Brain chemicals are depleted (especially the neurotransmitter, acetylcholine)

Factors that contribute to amyloid formation:
- Inflammation
- Oxidative stress
- Cholesterol

Factors that promote brain health:
- Estrogen Growth Factors
AD TREATMENT -- ANTI-AMYLOID STRATEGY

- Vaccination?
- Secretase inhibition?
- Dissolve aggregated beta-amyloid?
Anti-amyloid approach-vaccination

• Was done in genetically modified mice which develop amyloid plaques at about one year of age
• Prevention experiment: immunize every month from 1.5-12 months --> examine brain
• Treatment experiment: immunize every month from 11-18 months --> take brain
Beta-amyloid vaccination study

Schenck Nature 1999
Anti-amyloidoid strategies: vaccination

- Phase I trials—healthy subjects receiving a single beta-amyloid injection—looked safe
- Phase II study was aborted due to a minority of subjects developing encephalitis (2002)
- Trial of passive immunization with a monoclonal antibody directed against beta amyloid initiated 2005—results to be reported July 2008
Anti-amyloid strategies: secretase inhibition
Anti-amyloid strategies: secretase inhibition

- Beta-secretase and gamma secretase inhibitors have shown promise in animal models
- Lilly Phase 2 trials showed excellent tolerance of a gamma secretase inhibitor, with measurable effects on plasma beta amyloid
- Phase 3 trial starting 2008
Anti-amyloid strategies: solubilizing agents

- Beta amyloid is very insoluble—requires concentrated formic acid to dissolve it in vitro.
- However—compounds with “beta-breaker” activity can put fibrils back into solution.
- “Clioquinol”, an old antibiotic, showed efficacy in animal studies and in a pilot trial, but also has a history of neurotoxicity—
- “scylloinositol” is the latest “beta-breaker” to enter clinical trials—expect more in the future.
Dementia-pathophysiology meets pharmacology

<table>
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<tr>
<th>MECHANISM</th>
<th>STATUS</th>
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<tbody>
<tr>
<td>Cholinergic deficit</td>
<td>3 approved CEI’s</td>
</tr>
<tr>
<td>excitotoxicity</td>
<td>1 approved NMDA antagonist</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>Vitamin E recommended</td>
</tr>
<tr>
<td>Anti-inflammatory estrogen</td>
<td>Failed</td>
</tr>
<tr>
<td>Cholesterol-lowering</td>
<td>Failed</td>
</tr>
<tr>
<td>Anti-amyloid</td>
<td>Under study</td>
</tr>
</tbody>
</table>

**Note-this refers to treatment, not prevention**
Questions?