Cortical Dementias

Last updated: May 8, 2019

**ALZHEIMER’S DISEASE (AD)**

1. Alzheimer's Disease
2. Asymmetrical Cortical Degeneration Syndromes
3. ALS-Dementia Complex

**PATHOGENESIS, PATHOPHYSIOLOGY, PATHOLOGY**

AD is a disease process that ultimately results in Alzheimer's dementia.

- **old terminology**: Alzheimer's dementia (s. presenile dementia) buvo vadinami cases with onset before age 65; dementia developing after age 65 was called senile dementia – now there is consensus to consider both a single disease!
- history of AD began in 1907 with Alois Alzheimer's short medical report of 56-year-old woman whose brain he evaluated.
MACROSCOPY - variable degree of generalized **CORTICAL ATROPHY**.

- gyri narrowing, sulci widening and compensatory ventricular enlargement (“hydrocephalus ex vacuo”).
- brain weight ↓.
- diffuse, but most pronounced in *frontal, temporal, parietal* association cortices (sparing occipital lobe), *hippocampus, amygdala*.

Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)
Atrophy of temporal lobes:

Senile dementia. The brain shows diffuse cortical atrophy, particularly marked in the frontal, parietal and superior temporal lobes, with narrowing of the gyri and widening of the sulci.

**Mesial temporal structures** (particularly *hippocampal formation*) are involved early in AD → amnestic syndrome.

Damage to entorhinal cortex effectively *disconnects hippocampus from its major input and output pathways*!

**Microscopy** - widespread cortical:
1) intracellular *neurofibrillary tangles* (NFT)
2) extracellular *neuritic (senile) plaques* (NP)
3) *amyloid angiopathy*
   - N.B. these may be present (to lesser extent) in elderly nondemented individuals!!!
   - AD diagnosis is based on *combination of clinical and pathologic features*.
   [e.g. adequate number of NP present within specified age range in clinically demented patient]

- NFT and NP are relatively absent in primary motor and sensory cortices (i.e. primarily affect *association cortices*)!
- have LAMINAR DISTRIBUTION in cortex (primarily affect *medium-sized pyramidal neurons* in lamina III and IV effecting cortico-cortical connections).
**Neurofibrillary Tangles (NFT)** - bundles of interwoven neuron cytoplasm processes (filaments) that displace or encircle nucleus.

- commonly found in cortical neurons (esp. in entorhinal cortex).

**NFT are characteristic but not specific to Alzheimer disease** (also found in progressive supranuclear palsy, postencephalitic Parkinson disease, amyotrophic lateral sclerosis-parkinsonism/dementia complex of Guam)

- NFT represent endpoint of number of different cellular pathophysiologic processes - manifestation of abnormal organization of cytoskeletal elements.
- NFTs even in small numbers should be considered abnormal! (vs. NP – may be found in normal aged persons).

Neurofibrillary tangles:

A. H&E – as basophilic fibrillary structures (arrowheads).

B. Silver stain (Bielschowsky) – best visualization!

Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)
• elongated "flame" shape; in some cells, basket weave around nucleus takes on rounded contour (globose tangles).
• insoluble and difficult to proteolyze in vivo - visible as "ghost" or "tombstone" tangles long after death of parent neuron.
ULTRASTRUCTURE - paired helical filaments along with some straight filaments.

- composition of paired and straight filaments is comparable.
- components:
  1) major component - abnormally hyperphosphorylated forms of TAU protein (axonal microtubule-associated protein that when dephosphorylated enhances microtubule assembly).
    - gene on chromosome 17.
    - hyperphosphorylated TAU destabilizes microtubules → disrupted axonal transport → NFT formation → neuronal death
  2) MAP2 (another microtubule-associated protein)
  3) ubiquitin
  4) amyloid beta-peptide (Aβ).
- paired helical filaments are also found in:
  - dystrophic neurites of NEURITIC PLAQUES;
  - axons coursing through affected gray matter (NEUROPIl THREADS).

NEURITIC (senile) plaques (NP) - focal, spherical collections of dilated, tortuous axonal endings (DYSTROPHIC NEURITES) surrounding central AMYLOID CORE, often surrounded by clear halo.

- found in hippocampus and amygdala as well as in neocortex.
- range in diameter 20-200 μm.
- microglial and reactive astrocytes are present at periphery.
A senile (neuritic) plaque composed of a central, silver-positive amyloid core surrounded by a ring of cellular processes (Bielschowsky stain).
Thioflavin stain viewed with fluorescence microscopy - highlighted neuritic plaques with amyloid deposition (arrow) which fluoresces bright green:

- **DYSTROPHIC NEURITES** (best stained with Bielschowsky silver stain) contain **paired helical filaments**, synaptic vesicles, abnormal mitochondria.
- **AMYLOID CORE** contains several abnormal proteins:
  1) dominant component - **amyloid beta-peptide (Aβ)**
  2) alpha1-antichymotrypsin
  3) apolipoproteins
  4) protein termed non-amyloid component of plaques (NACP).

**Amyloid cascade:**
1. **DIFFUSE NON- NP** - DIFFUSE amyloid deposition *without surrounding neuritic reaction* (such plaques are present in normal aged persons [senile plaques] and Down’s syndrome patients).
2. **DIFFUSE NP** - appearance of distended neurites.
3. **Dense-core NP** (equivalent to classic NP) - *Insoluble* amyloid fibrils surrounded by distended neurites constitute.

4. "**Burnt-out** Plaque" - dense core of amyloid without surrounding distended neurites.

**Amyloid Angiopathy** - invariable accompaniment of AD!
- Vascular amyloid is derived from same precursor as NP amyloid cores (i.e. APP).

Congo red staining of cerebral cortex: amyloid deposition in blood vessels + amyloid core of neuritic plaque (arrow):
Granulovacuolar degeneration (of Shimkowicz) - small (5 μm), clear intracytoplasmic vacuoles, each of which contains argyrophilic granule.
- found almost exclusively in hippocampus (also occurs with normal aging).

Hirano bodies - elongated (rod-like), glassy, eosinophilic bodies in hippocampus (along pyramidal cells).
- consist of paracrystalline arrays of beaded filaments (with actin as major component).

Neuropil threads - dystrophic neurites diffusely distributed in cortical neuropil (more or less independently of plaques and tangles) - third location of paired helical filaments outside of NFT and NP.

Correlates of clinical degree of dementia

Histologic - number of neurofibrillary tangles (correlates better than number of neuritic plaques).
- Synapse loss (with neuronal loss) appears to be most important correlate of dementia severity!

Biochemical:
1) loss of choline acetyltransferase
2) synaptophysin immunoreactivity
3) amyloid burden.

Amyloid beta peptide (Aβ)
- although amyloid-rich plaques correlate less well with clinical disease than do neurofibrillary tangles, amyloid has relative specificity for AD (esp. familial AD).
Aβ is derived from larger molecule, **amyloid precursor protein (APP):**

APP is normally expressed in multiple cells of neural and non-neural origin. APP is transmembrane protein of uncertain cellular function. 

Expressed on cell surface APP can be processed:

a) **α-secretase** → soluble secreted APPs (nonamyloidogenic pathway - cannot give rise to Aβ).

b) reinternalized into endosomes → β and γ-secretases* → soluble Aβ → aggregation into amyloid fibrils.

*there is mild variation in proteolysis endpoints - two predominant species are generated: **Aβ40** (40 amino acids) > **Aβ42** (42 amino acids);

- levels of each can be measured in both plasma and CSF;
- insoluble Aβ42 form is contained in plaques.

- Aβ and its aggregates are **neurotoxic** in vitro (Aβ may promote free radical formation - OXIDATIVE STRESS HYPOTHESIS of neurodegeneration).
- **APP gene** is on chromosome 21.
- several forms of familial AD are linked to **APP gene** mutations - lead to increased Aβ production.

**Initial abnormality in AD pathogenesis** is neurotoxic amyloid (mainly Aβ42) deposition in neuropil (forming plaques) and cerebral vessels (forming amyloid angiopathy) → cytoskeletal derangement → neurofibrillary tangle formation → neuronal degeneration.

- it is hoped that interfering with Aβ42 formation / deposition may impact AD pathogenesis.

**Presenilins**

- **chromosomes 14** and **1** have genetic loci linked to majority of early-onset familial AD pedigrees (mean onset before age 50).
- genes (on these two chromosomes) encode highly related intracellular proteins - presenilin-1 and presenilin-2.
- role of presenilins:
  1) both presenilins are related to γ-secretase activity - mutations in presenilins increase Aβ production (esp. Aβ42).
  2) presenilins are targets of caspase proteases activated during apoptosis (role in neuronal cell death).

**Apolipoprotein E**

- one allele (ε4) of **ApoE gene** on chromosome 19 increases AD risk and lowers age at onset.
- ApoE can bind **TAU protein** - prevents formation of NFT; ε4 binds less efficiently → ↑susceptibility to sporadic AD.
- ApoE can bind Aβ (promotes amyloid filament formation in vitro); ApoE reduces brain's ability to rid itself of amyloid beta.
- ApoE is present in plaques, tangles and vascular amyloid.

N.B. ε4 does not directly cause AD and disease progression is not associated with ApoE status! Many AD patients have no ε4 allele!
• ε2 allele decreases risk and increases age of onset!

**NEUROTRANSMITTERS**

Levels reduced: acetylcholine, noradrenaline, serotonin, GABA, glutamate, somatostatin, neuropeptide Y, substance P.

N.B. reductions in **acetylcholine** and **choline acetyltransferase** are the most profound - due to **neuronal loss in BASAL FOREBRAIN** (major region from which cholinergic projections originate).

*esp. nucleus basalis of Meynert

**CHOLINERGIC AGONISTS** → only modest improvement in cognitive functions (due to neuronal loss in cortical targets that receive cholinergic input).

• nucleus locus ceruleus (noradrenergic) degeneration.
• nucleus raphe dorsalis (serotonergic) degeneration.

**GENETICS**

At least 5-10% of cases are familial! – **AUTOSOMAL DOMINANT:**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Mutations/Alleles</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Amyloid precursor protein (APP)</td>
<td>Single or double missense mutations; Trisomy 21 (gene dosage effect)</td>
<td>Early-onset familial AD (AD1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aβ production↑</td>
</tr>
<tr>
<td>14</td>
<td>Presenilin-1 (PS1)</td>
<td>Missense or splice site mutations</td>
<td>Early-onset familial AD (AD3) – 70-75% of all early-onset familial AD cases</td>
</tr>
<tr>
<td>----</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aβ production↑</td>
</tr>
<tr>
<td>1</td>
<td>Presenilin-2 (PS2)</td>
<td>Missense mutations</td>
<td>Early-onset familial AD (AD4) - families of Volga German ancestry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aβ production↑</td>
</tr>
<tr>
<td>12</td>
<td>Another protein</td>
<td>(currently under study)</td>
<td>Late-onset familial AD</td>
</tr>
<tr>
<td>19</td>
<td>Apolipoprotein E</td>
<td>Allele ε4</td>
<td>Increased risk of sporadic AD with decreased age at onset (AD2?). Also associated with atherosclerosis and cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>(ApoE)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Protocadherin 11 X-linked (PCDH11X) - receptors involved in cell-cell adhesion and signaling</td>
<td>Late-onset familial AD</td>
<td></td>
</tr>
</tbody>
</table>

*best established late-onset familial AD susceptibility allele

**Concordance rates** among monozygotic twins are 40-60% - suggesting strong but not absolute genetic influence (i.e. strong environmental influence!)
- genetiką tyrinėti sunku, nes susergama vėlyvame amžiuje.

**DOWN'S SYNDROME has strong association with AD**
- if patient with Down's syndrome lives beyond 40-45 years, it will have AD neuropathology at autopsy.
- trisomy 21 predisposes to larger plaques* (reflecting increased Aβ production)

* vs. ApoE ε4 leads to greater numbers of plaques (reflecting increased plaque initiation).

### EPIDEMIOLOGY

- AD is most common cause of dementia overall (50-70% of all cases).
- AD ranks 4th as cause of death in USA! (after heart disease, cancer, and stroke)

### RISK FACTORS

1. **Advancing age** - leading risk factor - **exponential increase** at least through ninth decade.
   - prevalence of severe dementia:
     - 65-74 years – 3%
     - 75-84 years – 19%
     - > 85 years – 47%
   - lifetime risk of developing AD is **12-17%**.
   - some studies suggest that risk of AD decreases in individuals older than 80 or 90 years!

2. **ApoE status** - second most important risk factor (ε4 allele increases risk*, ε2 allele decreases risk).
   - lifetime risk (in people without family history):
     - no ε4 – 9%
     - one copy of ε4 – 29%
     - ε4 homozygote (≈ 2% of population) – 83%.

* dose-dependent modifier of age of AD onset
3. **Other genetic factors**: Down's syndrome (trisomy 21), kindreds of familial early-onset AD (chromosomes 14, 1)

4. **Subjective memory impairment (SMI)** at baseline, especially if accompanied by **worry**.

5. **Other purported weaker risk factors**:
   1. gender (**women** : **men** = 2 : 1 – due to loss of neurotrophic estrogen effect in postmenopause)
   2. estrogen replacement therapy (protective)
   3. vitamin E (protective), anti-inflammatory drugs (protective)
   4. limited education
   5. depression
   6. head trauma
   7. history of thyroid disease.

N.B. at present, **aluminum exposure** is not thought to be major risk factor for AD!

### CLINICAL FEATURES

**CLINICAL COURSE**

- **ONSET** – insidious; symptoms appear after age 50 (**early-onset** – before age 50).
- **COURSE** - slowly steadily progressive (**plateaus** sometimes occur during which cognitive impairment does not change for year or two, but progression then resumes), vs. step-wise deterioration in multi-infarct dementia.

**Alzheimer’s Disease Assessment Scale-Cognitive** (ADAS-Cog; range 0 to 70) is commonly used performance test; on average, patient declines ≈ 8 points per year on this scale.

**CORTICAL DEMENTIA SYNDROME** - not only **memory loss** (common to many dementia syndromes), but also elements of **aphasia, apraxia, agnosia, acalculia**.

- absence of **subcortical features** (such as parkinsonism); but in advanced stages patients often look parkinsonian (due to muscle tone↑, shuffling gait).

NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association) Work Group’s **diagnostic criteria for AD**:

<table>
<thead>
<tr>
<th>I. Clinical diagnosis of <strong>PROBABLE AD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Dementia</strong> (established by clinical examination and mental status testing; confirmed by neuropsychological testing)</td>
</tr>
<tr>
<td>2. Deficits in <strong>at least two cognitive domains</strong></td>
</tr>
<tr>
<td>3. <strong>Progressive</strong> cognitive decline, including memory</td>
</tr>
<tr>
<td>4. <strong>Normal level of consciousness</strong></td>
</tr>
<tr>
<td>5. <strong>Onset</strong> between ages 40 and 90 (most common after 65) years</td>
</tr>
<tr>
<td>6. <strong>No other possible</strong> medical or neurological <strong>explanation</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. <strong>PROBABLE AD</strong> diagnosis supported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Progressive aphasia, apraxia, and agnosia</td>
</tr>
<tr>
<td>2. Impaired activities of daily living</td>
</tr>
<tr>
<td>3. Family history of similar disorder</td>
</tr>
<tr>
<td>4. Brain atrophy on CT/MRI (especially if progressive)</td>
</tr>
</tbody>
</table>
5. Normal CSF, EEG (or nonspecifically abnormal)

### III. Other clinical features consistent with PROBABLE AD

1. Plateau in course

2. Associated symptoms: depression; insomnia; incontinence; illusions; hallucinations, catastrophic verbal, emotional, or physical outbursts; sexual disorders; weight loss; during advanced stages - increased muscle tone, myoclonus, abnormal gait.

3. Seizures in advanced disease

4. CT normal for age

### IV. Features that make AD Uncertain or Unlikely

1. Acute onset

2. Focal sensorimotor signs

3. Seizures or gait disorder early in course

### V. Clinical diagnosis of POSSIBLE AD

1. Atypical dementia in absence of another medical/neuropsychiatric explanation

2. Dementia with another disease not felt otherwise to be cause of dementia

3. For research purposes, progressive focal cognitive deficit

### VI. DEFINITE AD

1. Meets clinical criteria for PROBABLE AD

2. Tissue confirmation (autopsy or brain biopsy)

### VII. Research Classification of AD should specify:

1. Familial?

2. Early onset (before age 65)?

3. Down's syndrome (trisomy 21)?

4. Coexistent other neurodegenerative disease (e.g. Parkinson's disease) ?

N.B. DEFINITE AD is defined by tissue confirmation!

Without histological confirmation, clinical picture of dementia is the most important diagnostic feature:

**PROBABLE AD** = clinical picture of dementia + no atypical features + another cause cannot be found.

**POSSIBLE AD** = clinical picture of dementia + atypical features / second potentially contributory disease not believed to be primary cause.

Overall clinical-pathological correlation of Alzheimer's dementia with AD is now $\approx 87\%$

ALZHEIMER'S DEMENTIA is defined as cortical dementia with specific pattern and evolution of cognitive deficits (rarely, pathologically defined AD may not present in this way!):

begins with mild, slowly progressive memory disorder, with other spheres of cognitive impairment added over course of several years

**I. Memory loss** - earliest and cardinal clinical sign of AD!!!
- **abnormal cerebral metabolism**, demonstrated by PET, may precede even mild memory loss.
- **RECENT memory** is disproportionately severely involved → confusion.
- **REMOTE memory** is also abnormal; GRADIENT EFFECT - oldest memories are best preserved, with proportionately greater forgetting as retrograde interval shortens.
- **PROCEDURAL (NONDECLARATIVE) memory** is relatively spared - patients are able to learn simple skills as easily as normal controls (and better than patients with subcortical dementia or patients with various sensorimotor deficits).
- **DRIVING**: despite relative preservation of procedural memory, patients with mild Alzheimer's dementia have higher rate of collisions and moving violations.
- subset of patients present with circumscribed, slowly progressive amnesic syndrome, referred to as "age-associated memory impairment" (AAMI) - these patients should be distinguished from milder memory problems of normal aging; ≈ half of AAMI patients develop dementia over 4-5 year period.
  N.B. although new memory retention decreases with age, other cognitive functions remain relatively intact!

**Aphasia, apraxia, and agnosia** are typical to cortical dementia syndromes (and particularly to AD), but in Alzheimer's dementia, these aspects do not dominate clinical picture.

**II. Aphasia**
- in mild stages, **ANOMIA** is prominent and readily detectable.
- as disease progresses, predominantly anomic aphasia gives way to more fluent (WERNICKE type) aphasia with impaired comprehension.

N.B. **NONFLUENT aphasia does not generally occur in AD** (although preterminal nonambulatory patients become mute).

**III. Apraxia**
- trouble dressing and performing other activities of daily living.
- rarely severe in mild to moderate stages of AD - can be confused with impaired comprehension.

**IV. Agnosia**
1. **ANOSOGNOSIA** (lack of insight) - cardinal feature of Alzheimer's dementia!!! - typically present, even in mild stages.
   - typical AD patient is brought or sent for evaluation rather than coming of his or her own accord.
   - patient denies significant memory problems and will actively try to explain away observations of concerned family members and friends, even to point of becoming hostile and accusative.
   - one of most difficult disease aspects - patients should not be driving or managing their own finances but will do so anyway, sometimes to their detriment.
2. **PROSOPAGNOSIA** (not reliably benefited by voice recognition either).
3. **ATOPOGRAPHAGNOSIA** (difficulty finding way - tendency to get lost in familiar surroundings – another cardinal feature of Alzheimer's dementia!!!).
4. **ASIMULTANAGNOSIA** (inability to view all parts of complex visual scene in single coherent time-space frame); patients fail to see target object that is right in front of them, especially if it is surrounded by distracting stray objects.

Important contributing factor is **VISUAL-SPATIAL DISORIENTATION**.

**V. Psychiatric symptoms**
1. **DEPRESSION** may complicate AD course (≈ 50% patients), esp. if patient retains some insight.
interferes with accurate cognitive assessment (clinical depression may mask dementia and vice versa!)
antidepressant therapy should be strongly considered.

2. **Psychotic Symptoms**
   - most commonly (≈ 20%) - **paranoid delusions** (common themes involve infidelity and stealing).
   - less commonly – **hallucinations** (generally complex, involving people (familiar or unfamiliar), animals).
   
   N.B. AD should be in differential diagnosis of elderly patient presenting de novo with organic delusional syndrome or hallucinosis!

3. Slowly progressive **personality-behavioral changes** (wandering, irritability, hostility, agitation, uncooperativeness, physical aggressiveness, apathy).

**VI. Vegetative symptoms**

1. **Sleep-Wake Cycle Disturbances** are common (may be present even during relatively mild stages of illness):
   1) **Sundowning effect** - patient becomes more confused, agitated, and difficult to manage during evening hours.
   2) **Sleep Fractionation** - not sleeping at night, waking up during very early hours, going to sleep very early in evening.
   3) Prolonged **daytime, deep-sleep states** may occur during which patient cannot easily be aroused.

   as disease progresses, patients become generally less active, sleep more, and in terminal stages, are bedbound with little apparent conscious activity.

2. **Incontinence** (both **urinary** and **fecal**) becomes increasingly frequent as disease progresses (universal in late stages) - early it is *voiding in "wrong place"*, but in later stages, *sphincter control is lost*.

   N.B. incontinence and gait dyspraxia early in course suggests normal pressure hydrocephalus!

**Terminal Stage**

- death ensues after roughly 5-10 year* course (course is slow but relentless).

   *course can range from 1 to 25 years

   - patient becomes totally dependent on caregiver - immobile, wasted, mute and incontinent;
   
   spasticity and seizures are common.
   
   N.B. financial and legal arrangements (e.g. durable power of attorney) should be made in early stage of disease when patient is still competent!

   - **dysphagia** signals terminal phase - unless **feeding tube** is placed, patients die from **inanition** or aspiration.

   N.B. few patients live to these stages, with death resulting from **intercurrent illnesses** (esp. aspiration pneumonia, UTI) in most.

   AD itself is not the most common cause of death!

**Differential Diagnosis**

Realistic differential diagnosis includes:

1. **Other degenerative diseases** - Pick's disease, nonspecific degeneration (progressive subcortical gliosis), diffuse Lewy body disease.

2. **Vascular dementia**.
• in early stages, clinical cognitive patterns can be very helpful in distinguishing various dementing illnesses.
• in late stages, patients are diffusely impaired (both cognitively and somatically) - difficult to tell one degenerative brain disease from another.

**DIAGNOSTIC EVALUATION**

Although **PATHOLOGIC EXAMINATION of brain tissue** is necessary for definitive diagnosis, combination of **CLINICAL assessment** and modern **NEUROIMAGING** allows accurate diagnosis in 80-90% of cases.

• **neurologic examination** is normal! (until advanced stage)

**COGNITIVE EXAMINATION** is essential.

• **mini-mental status test (Folstein)** score is < 20; benign forgetfulness of senility generally scores > 25.
• **neuropsychological assessment** is highly desirable in mild to moderate stages.
  • typical neuropsychological profile:
    – reduced performance IQ relative to verbal IQ
    – severe learning and memory impairment
    – anomia, impaired aural comprehension
    – psychomotor speed is generally preserved.

AD is very underdiagnosed disease - incorporate **mini-mental status test** into routine examination of all older persons!!!

**NEUROIMAGING** is essential.

• **MRI** is preferred, but **CT** is generally adequate.
  – CORTICAL ATROPHY - generalized (initially - bilateral medial temporal, including hippocampus); nonspecific and (in absence of quantitation) is difficult to use for diagnostic purposes (esp. in elderly – mild atrophy is normal!).
  – atrophy of hippocampus & entorhinal cortex can be demonstrated by MRI up to 2 years before definitive diagnosis can be made.
• functional neuroimaging is not recommended for routine evaluation;
  – SPECT and PET show bilateral parietal (temporoparietal & posterior cingulate) HYPOMETABOLISM / HYPOPERFUSION:
CORTICAL DEMENTIAS

- relative preservation of calcarine fissure region, sensory-motor region, cerebellum, and basal ganglia region.

**AMYVID** (Florbetapir F 18), **VIAZMYL** (Flutemetamol F18) – FDA approved radioactive diagnostic agents for PET indicated for imaging of beta-amyloid plaques in patients with cognitive impairment who are being evaluated for Alzheimer's Disease and other causes of cognitive decline.

**NEURACEQ** (Florbetaben F18 injection) - FDA approved radioactive diagnostic agents for PET indicated for imaging of beta-amyloid plaques

**LABORATORY TESTS** should exclude reversible dementia causes. see p. S10

- EEG, CSF examination should be ≈ normal in degenerative diseases (incl. AD).
  - in CSF – TAU protein↑, Aβ42↓ (due to increased deposition) – but considerable overlap with normal limits and other neurodegenerative diseases!
  - in EEG – diffuse nonspecific slowing (uncommonly may be focal! – but suggests multi-infarct dementia or other multifocal cause).

### SCREENING

- **early-onset cases** may be screened for specific mutations on chromosomes 1, 14, and 21.
  - **GENETIC TESTING** cannot definitively determine diagnosis of AD!
- **typical cases** are linked to ApoE ε4 allele.
  - **ApoE TESTING** (commercially available) is not yet appropriate for clinical use due to controversial ethical issues (e.g. whether information should be available to patient, family members, or insurers when information does not define disease).
  - ApoE testing *does not have predictive value* for asymptomatic individuals!!!

### MANAGEMENT

**FDA APPROVED DRUGS**

**Centrally acting ACETYLCHOLINESTERASE INHIBITORS** (reversible, noncompetitive):

1. **TACRINE** (Cognex®)* - used rarely today (due to asymptomatic hepatotoxicity, inconvenient dosage)
2. **DONEPEZIL** (Aricept®)
3. **RIVASTIGMINE** (Exelon®)*
4. **GALANTAMINE** (Reminyl®, Razadyne®)

*also inhibit **BUTYRYLCHOLINESTERASE** (levels increased in AD) – beneficial therapeutically

<table>
<thead>
<tr>
<th>CHOLINESTERASES:</th>
</tr>
</thead>
<tbody>
<tr>
<td>synaptic (specific) - ACETYLCHOLINESTERASE</td>
</tr>
<tr>
<td>nonsynaptic (nonspecific) - BUTYRYLCHOLINESTERASE</td>
</tr>
</tbody>
</table>

- partially reverse decline in cortically projected (corticipetal) acetylcholine that results from degeneration of cholinergic basal forebrain.
- **the only drugs with possible cognitive enhancing effects** - FDA approved for mild to moderate stages of AD; but also significantly improve behavioral manifestations in advanced stages.
  - **DONEPEPZIL** – the only drug FDA approved for all degrees of Alzheimer dementia!
- do not influence AD progression!
CORTICAL DEMENTIAS

- **effects are modest** and **side effects are significant** (particularly at higher, more effective dosages)
  - nausea, diarrhea, dizziness, liver enzymes↑ \((TACRINE)\):
    - side effects are dose-related – can be mitigated by **slow upward dose titration**!
- **relative contraindications** - supraventricular cardiac conduction abnormalities, liver disease, seizures, asthma.
- once patient is started on cholinesterase inhibitor, it should be **continued indefinitely** (stopping medication may precipitate acute, severe cognitive and behavioral decline that may not be resolved by restarting medication!!!).

The number needed to treat for any benefit in patients with Alzheimer disease for donepezil (the most commonly prescribed cholinesterase inhibitor) is 12. \([27]\) This means that for every patient who obtains a modest benefit from this drug, 11 will be treated but have no benefit. The side effects are disturbing with this class of drugs and include nausea, decreased appetite, weight loss, syncope, and urinary incontinence. \([26,29]\) Some patients may even be started on an antimuscarinic agent for the urinary incontinence caused by the cholinesterase inhibitor they are taking.

**N-METHYL-D-ASPARTATE (NMDA) ANTAGONISTS:**
  - NMDA receptor stimulation by **glutamate** (excitatory amino acid) is hypothesized to contribute to Alzheimer symptoms.

**MEMANTINE** (Namenda®) - first NMDA antagonist approved in USA.
- FDA approved (incl. extended-release) for **moderate-severe stages** of AD.
- studies demonstrate long lasting (but modest) effect during continued use.
- may be combined with cholinesterase inhibitor.

**OTHER (NOT FDA APPROVED) DRUGS**

1. Free radical scavengers (based on proposal that AD is caused by oxidative stress):
   1) high doses of **TOCOPHEROL** (1000 IU PO bid)
   2) **Egb761** (extract of *Ginkgo biloba*) - lack of clear efficacy!!! (largest study found no efficacy!!!)
   3) **SELEGILINE**

2. **Estrogen** or selective estrogen receptor agonists (based on evidence that estrogen has trophic effect on certain neuronal populations) in postmenopausal women.

Experimental **INHIBITORS OF AMYLOID DEPOSITION:**

**CLIOQUINOLINE** - antibiotic that may reduce amyloid deposits.

**CONTROL OF SYMPTOMS**

N.B. **all** psychotropic drugs increase confusion and lethargy (and mortality over long term) – should be used at minimum doses and minimum duration!
“Risks and benefits of prescribing antipsychotics to patients with dementia need to be carefully balanced, and these drugs should only be used if alternative strategies do not work”

**Paranoid delusions & other psychotic symptoms** (not cognitive decline!) are most common reasons patients are sent to nursing homes!
Small doses of NEUROLEPTICS may produce sufficient relief as to permit caregivers to continue to keep patient at home:

1. **HALOPERIDOL** – not advisable due to side effects.
2. **RISPERIDONE** – additional effects on serotonergic systems and fewer extrapyramidal side effects.
3. **OLANZAPINE**
4. **QUETIAPINE**

**Depression** → SSRI.
- should not be used in agitation or psychotic symptoms - SRI can exacerbate these behaviors!
- antidepressants with anticholinergic side effects (incl. all tricyclics) exacerbate confusion!

**Agitation, anger outbursts, disruptive behaviors** – VALPROIC ACID, TRAZODONE, CARBAMAZEPINE, RISPERIDONE.

**Anxiety:**
- a) **BUSPIRONE**
- b) **BENZODIAZEPINES** (risk of paradoxical agitation).
- c) **NEUROLEPTIC** (if there are accompanying psychotic symptoms).

**Sleep-wake disturbances:**
1. **daytime** - increase activity and decrease daytime sleep (bright light exposure).
2. familiar surround at night.
3. **SEDATIVE HYPNOTICS** (trazodone, diphenhydramine, chloral hydrate, zolpidem, thioridazine).
4. neuroleptics are last resort.

**ACTIVITY**
Both **physical** and **mental** activities are recommended (in particular, many experts recommend MENTALLY CHALLENGING ACTIVITIES, such as crossword puzzles and brainteasers).
- keep patient's home safe and easy to navigate (e.g. lock unused doors, drawers).

**FOR CAREGIVERS**
Caregiver burden is high, and so **caregiver assessment should be included at each evaluation**.
Prepare family that one day patient won’t recognize them!
1. **Support groups**.
2. Help from Alzheimer's Association and local Alzheimer's disease centers!
3. **Respite care** (to give caregiver time away from patient – to prevent so common caregiver "burnout"), e.g. adult day care (useful as supervised social outlet for patient, too).

**FUTURE PERSPECTIVES**
Possible preventive & retardant strategies:
1) interfering with **amyloid/tau/ApoE pathway**.
2) administration of ApoE ε2.
3) growth factors (that normally function during embryogenesis - promote neuronal growth).
4) antioxidants (vitamin E).

There is no known way to entirely protect against AD!

**DBS**

The targets:

1. **Nucleus basalis of Meynert (NBM)** - most realistic target
   - combined bilateral stimulation lead to *improvement in attention, concentration, alertness, drive, and spontaneity* (Freund et al. 2009)
   - in Alzheimer disease patients, after 1 year of bilateral stimulation, ADAS-cog scores worsened by an average of 3 points (95% CI = −6.1 to 12.1 points, P = 0.5), the mean MMSE score remained almost stable (decreased by 0.3 points, 95% CI = −4.5 to 5.2 points, P = 0.9) – this is all is *slower cognitive decline* than in pharmacologically treated controls (Kuhn et al. 2015).
   - dementia is a progressive disease and there is likely a limited window of opportunity to stimulate the remaining NBM fibres before the nucleus becomes too degenerate for stimulation to enhance its output, therefore, patients may need to be implanted earlier in the disease course. Patients suitable for NBM DBS trials are likely to be those who have already tried cholinesterase inhibitors, have minimal cortical atrophy on imaging, lack significant co-morbidities and who have lucid intervals and capacity to consent.

2. **Fornix** – stimulation caused from *cognitive worsening* (Fontaine et al. 2013) to *possible improvements and/or slowing in the rate of cognitive decline* at 6 and 12 months in some patients (Laxton et al. 2010) to *significant improvements* on the California Verbal Learning Test and Spatial Associative Learning Test (Hamani et al. 2008).

3. **Entorhinal cortex** – stimulation caused *memory enhancement* (in virtual memory task) and theta-phase resetting (Suthana et al. 2012).

4. **Hippocampus** – bilateral stimulation was associated with a *pronounced decrease in memory* scores (Lacruz et al. 2010a,b); in epileptic patients, hippocampal single pulse stimulation might impair rather than facilitate memory functions (Halgren et al. 1985; Lacruz et al. 2010a) - stimulations might cause an acute depolarization block, which possibly disrupts formation and recall of recent episodic memory.

5. **Anterior thalamic nucleus** – no human data; some promising data in rats; in SANTE (epilepsy) trial, neuropsychological testing showed no group differences on cognitive functions, however significantly more participants of the stimulated group reported depression and *memory problems* as adverse events (Fisher et al. 2010).
<table>
<thead>
<tr>
<th>Structure</th>
<th>Subject</th>
<th>Type of stimulation</th>
<th>Memory task</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fornix</td>
<td>Human (morbid obesity patient) N = 1</td>
<td>Bilateral, 3.5–5V, 130 Hz and 60 μs pulse width, continuous for 3 weeks</td>
<td>Neuropsychological tests, e.g. verbal learning test, WAIS attention index, spatial associative learning, etc.</td>
<td>Significant improvements on the California Verbal Learning Test and Spatial Associate Learning Test</td>
<td>Hamani et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Human (AD patients) N = 6</td>
<td>Bilateral, 3.0–3.5 V, 130 Hz, and 90 μs pulse width, continuous for 12 months</td>
<td>ADAS-cog, MMSE</td>
<td>Possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients</td>
<td>Laxton et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Human (AD patient) N = 1</td>
<td>Bilateral, 2.5 V, 130 Hz and 210 μs pulse width, continuous for 12 month</td>
<td>ADAS-cog, MMSE, Free and Cued Selective Reminding Test</td>
<td>Cognitive scores worsened after 6 months but returned to baseline after 12 months of chronic DBS</td>
<td>Fontaine et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>Rats (model of experimental dementia) N = 10</td>
<td>Bilateral, 100 and 200 μA, 10 and 100 Hz, 100 μs pulse width, acute stimulation</td>
<td>OLT</td>
<td>Memory enhancement in high current densities (frequency-independent)</td>
<td>Hescham et al. (2013)</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>Mice N = 25</td>
<td>Bilateral, 50 μA, 130 Hz and 90 μs pulse width, for 1 h during surgery</td>
<td>Morris water maze</td>
<td>Water-maze memory was facilitated 6 weeks after stimulation due to hippocampus-dependent neurogenesis</td>
<td>Stone et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Human (epilepsy patients) N = 7</td>
<td>Bilateral, 0.5 to 1.5 mA, 50–130 Hz and 300–400 μs pulse width, cycle of 5 s on and 5 s off</td>
<td>Virtual memory task</td>
<td>Memory enhancement and theta-phase resetting</td>
<td>Suthana et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>Ncl. Basalis Meynert (NBM) Human (senile dementia of Alzheimer’s type patient) N = 1</td>
<td>Unilateral, 3 V, 50 Hz and 210 μs pulse width, cycling between 15 s on and 12 min off throughout the day and night, repetitive for 9 months</td>
<td>No clinical effect, but increased cerebral glucose metabolism</td>
<td></td>
<td>Turnbull et al. (1985)</td>
</tr>
<tr>
<td></td>
<td>Human (Parkinson patient) N = 1</td>
<td>NBM: Bilateral, 1 V, 20 Hz, and 120 μs pulse width STN: Bilateral, 3.5–4.2 V, 130 Hz and 60 μs pulse width</td>
<td>Neuropsychological tests, e.g. clock drawing, letter-number-span, auditory verbal learning, etc.</td>
<td>Combined bilateral stimulation lead to improvement in attention, concentration, alertness, drive, and spontaneity</td>
<td>Freund et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Rats N = 10</td>
<td>Unilateral, 200 μA, 50 Hz, and 0.5 ms pulse width, duration of 100 min</td>
<td></td>
<td>In adult, but not aged rats, NGF levels were significantly increased</td>
<td>Hotza et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Rats N = 4</td>
<td>Bilateral, 2.5 V, 130 Hz and 90 μs pulse width, duration 1 h</td>
<td>High-frequency stimulation of the ANT restores corticosterone-suppressed hippocampal neurogenesis</td>
<td></td>
<td>Toda et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Rats N = 12</td>
<td>Bilateral, 500 μA, 130 Hz and 90 μs pulse width, acute stimulation</td>
<td>Contextual fear conditioning, spatial alternating test</td>
<td>High frequency stimulation of 500 μA disrupted the acquisition of contextual fear conditioning and impaired spatial memory</td>
<td>Hamani et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Rats N = 17</td>
<td>Bilateral, 2.5 V, 130 Hz and 90 μs pulse width, duration 1 h</td>
<td>Non-matching-to-Sample and delayed non-matching-to-sample</td>
<td>ANT stimulation administered to corticosterone-created rats one month prior to testing improved performance on a delayed non-matching to sample task and increased hippocampal neurogenesis</td>
<td>Hamani et al. (2011)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Human (epileptic patients) N = 12</td>
<td>Bilateral, 4–6 mA, single pulse, 1 ms pulse width</td>
<td>Computerized recognition test</td>
<td>Bilateral stimulation was associated with a pronounced decrease in memory scores</td>
<td>Lacruz et al. (2010a,b)</td>
</tr>
</tbody>
</table>

Table 1 from Hescham et al. (2013)

The potential mechanisms involved in enhancing memory functions by DBS. Stimulation of a target area within the memory circuit (e.g. fornix) can provoke NGF release in the NBM, hippocampal-dependent neurogenesis, neural hijacking by resetting theta activity and increased acetylcholine release within the hippocampal region:
ASYMMETRICAL CORTICAL DEGENERATION SYNDROMES

- heterogeneous group of disorders that produce distinctive cortical syndromes (aphasia, apraxia, agnosia) but that have more focal appearance than AD.

PATHOGENESIS & PATHOPHYSIOLOGY

- NONSPECIFIC DEGENERATIVE CHANGES are common to all clinical subtypes and account for overall majority of pathological findings:
  1) neuronal loss
  2) reactive gliosis
  3) vacuolation (spongiosis) of neuropil predominantly affecting superficial cortical laminae.

- three properties of ATROPHY topography:
  1) lateralized major atrophic focus
  2) contralateral less severe focal atrophy area (asymmetry!)
  3) milder generalized atrophy.

CLINICAL FEATURES

- CLINICAL PRESENTATION is dictated by topographical distribution of degeneration.
- four primary categories:
  1) PROGRESSIVE APHASIA (left perisylvian area)
  2) PROGRESSIVE FRONTAL LOBE/Frontotemporal Syndromes (incl. Pick’s disease)
3) **PROGRESSIVE PERCEPTUAL** (typically visual) and **MOTOR** (typically hemiakinetic rigid) SYNDROMES

4) **PROGRESSIVE BITEMPORAL SYNDROMES**

- subtypes may overlap in the same patient.
- patients are usually **aware of their limitations** and are not likely to get themselves in trouble unwittingly by wandering, refusing medications, and so forth; they require nursing home placement less often.
- all are progressive and follow similar time course to AD.
- **late-stage complications** are similar to AD.

### PROGRESSIVE VISUAL SYNDROMES

- **visual association cortices** can be broadly divided:
  1. **Dorsal (occipitoparietal) pathway** - more concerned with localizing object in space (where); lesion → **asimultanagnosia**.
  2. **Ventral (occipitotemporal) pathway** - more concerned with object identification (what); lesion → **visual agnosia** (prosopagnosia, atopographagnosia).

### DIFFERENTIAL DIAGNOSIS

1. Slowly growing tumor
2. High-grade arterial stenoses cause stuttering infarction (mimicking slowly progressive degenerative cortical syndrome)
3. Abscess.

### EVALUATION

Most important diagnostic test is **adequate STRUCTURAL NEUROIMAGING** (**MRI** is preferable to **CT**) - focal **ATROPHY** in symptomatic region.

- **MRA** could be included to search for high-grade arterial stenosis.

Formal **NEUROPSYCHOLOGICAL ASSESSMENT** demonstrates pattern that is not typical for Alzheimer's dementia.

### MANAGEMENT

≈ similar to AD.

### PICK’S DISEASE (FRONTOTEMPORAL DEMENTIA)

- described by Arnold Pick in 1906.
- occurs almost entirely in presenium (45-65 years)
- incidence is < 2% that of Alzheimer disease.

### PATHOLOGY

#### MACROSCOPY

- **severe*** lobar atrophy of **FRONTAL and TEMPORAL lobes**.
* gyri reduced to thin wafer ("knife-edge" appearance).

- atrophy is frequently **asymmetric**!!!
- conspicuous sparing of:
  1) posterior two thirds of superior temporal gyrus.
  2) parietal - occipital lobes.
  3) basal forebrain.
- often bilateral atrophy of **caudate nucleus & putamen, hippocampus**.

Marked atrophy with ex vacuo ventricular dilation:
MICROSCOPY

- neuronal loss is most severe in **outer three layers** of cortex.
- reactive **glial proliferation** is prominent in both gray and white matter.
- surviving neurons are swollen, ballooned, poorly staining (chromatolytic) - **Pick cells**.
- surviving neurons contain pathognomonic **Pick bodies**.

  **Pick bodies** - cytoplasmic, round-oval, filamentous inclusions.
  - weakly eosinophilic but strongly argentophilic (appear densely black).
  - composed of **straight filaments**, vesiculated endoplasmic reticulum, and **paired helical filaments** (similar to Alzheimer disease).
  - Pick bodies **do not survive death of host neuron** - do not remain as disease markers (vs. neurofibrillary tangles of AD).
PATHOLOGICAL VARIETIES:
Pick's disease Type A – Pick cells and Pick bodies present.
Pick's disease Type B – no Pick bodies.
Pick's disease Type C, or nonspecific degeneration – no Pick cells, no Pick bodies.

- genetics - few kindreds with autosomal dominant Pick's disease, but no chromosome has been identified to date (TAU protein gene in chromosome 17?).

CLINICAL FEATURES
- memory problems and dementia in context of PROGRESSIVE FOCAL SYMPTOMS:
  1. FRONTAL lobe signs - behavioral changes, alterations in personality:
     1) abulia, apathy - fail to change clothes, to brush teeth, to pursue former interests, and to initiate many activities that constitute normal day;
just as they fail to start something new, patients may fail to stop what they are doing - perseveratively fixate on some particular activity (such as going to bathroom, sorting through their wallet, watching TV);

– may complain that they are hungry yet be unmoved to fix themselves a snack (some perseveratively want to eat over and over - bulimia).

2) **disinhibition & emotional lability** - crying at least provocation, or laughing loud and long.

3) hyperorality

4) spasticity - late in course (degeneration of primary motor cortex).

5) nonfluent aphasia

2. **TEMPORAL lobe signs** - **language disturbances** (esp. naming!).

<table>
<thead>
<tr>
<th>Behavioral problems</th>
<th>are early cardinal features of disease (rarely, can progress to psychosis)!</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>follows several years later</td>
</tr>
</tbody>
</table>

- patient answers are brief, and often consist of "I don't know".
- patients stick close to their caregiver and generally cause fewer disruptions than patients with AD.
- patients are visuospatial intact (vs. AD).
- patients may be not easily separable clinically from subjects with Alzheimer's disease.

N.B. consensus is that **differential diagnosis can be made only at BIOPSY and NECROPSY**!

i.e. neuroimaging finding of severe frontal and partial temporal atrophy alone may suggest, but would not prove, diagnosis in absence of histologic confirmation.

- course is similar to Alzheimer disease.

**DIAGNOSIS**

Suggested by imaging, confirmed histologically.

- **PET** - glucose metabolism↓↓↓ within frontal and temporal lobes.

T2-weighted turbo inversion recovery magnitude sequences - mild frontal atrophy:
**TREATMENT**

- no effective TREATMENT.

**BIBLIOGRAPHY**


McPhee, Lingappa, Ganong “LANGE Pathophysiology of Disease”, 2002

eMedicine (Alzheimer’s disease)

Weiner “Neurology (House Officer Series)”, 5th ed., 1994 (60-68 p.)


Rakel “Conn's Current Therapy 2000”, 52nd ed. (844-847 p.)


Cortical Dementias

“Harrison's Principles of Internal Medicine”, 1998
WebPath
Underwood “General and Systematic Pathology”, 1992 (780-781 p.)
“Oxford Handbook of Clinical Medicine” 1994
“Oxford Handbook of Clinical Specialties” 1995

Viktor’s Notes™ for the Neurosurgery Resident
Please visit website at www.NeurosurgeryResident.net