Phenomenology

Dementia is a disorder of cognitive function that can affect attention and concentration, language function, memory, visuospatial ability, perceptual ability, conceptualization and abstract reasoning, and general intelligence. You should be able to distinguish between cortical and subcortical dementias.

**CORTICAL DEMENTIAS**
reflect dysfunction of the cerebral cortex, and are characterized by amnesia, aphasia, apraxia, and agnosia. Classic example is Alzheimer’s disease.

**SUBCORTICAL DEMENTIAS**
reflect dysfunction of the deep gray and deep white matter structures, including the basal ganglia, thalamus, brain-stem nuclei, and the frontal lobe projections of these structures. They are characterized by disorders of arousal, attention, motivation, and the rate of information processing; this manifests clinically as psychomotor retardation, defective recall, poor abstraction and strategy formation, and mood and personality alterations such as depression and apathy. Classic example is Parkinson’s disease. Other examples include HIV dementia and Huntington’s disease.

Epidemiology

Dementia affects between 2-4 million Americans.
5-7% of those over 65
20% of those over 80
Neuritic Plaques are clusters of granular or filamentous materials with dense argyrophilic core. They are composed of amyloid and mucopolysaccharides and located throughout the cortex, but especially in the frontal, hippocampal and parahippocampal areas.

Neurofibrillary tangles are normally present in the brain.

There is a familial variety of Alzheimer’s. It is a rare form of Alzheimer’s, with an early onset (mid 50’s) and an an

Different types

<table>
<thead>
<tr>
<th></th>
<th>Percent of Dementias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>50%</td>
</tr>
<tr>
<td>Mixed</td>
<td>15-20%</td>
</tr>
<tr>
<td>Vascular</td>
<td>17-29%</td>
</tr>
<tr>
<td>Pick’s</td>
<td>13-16%</td>
</tr>
<tr>
<td>Alcoholic Dementia</td>
<td>7%</td>
</tr>
</tbody>
</table>

Other dementias include Creutzfeldt-Jakob (rare: <1/100,000) and Parkinson’s, in which dementia occurs in 25-40% of cases.

Pathology and Etiology

Alzheimer’s Pathology
is characterized by neuritic plaques, neurofibrillary tangles, and granulovacuolar degeneration.

Alzheimer’s Etiology
is unknown. Some hypotheses include:
Acetylcholine (ACh)
decrease in ACH
selectively degeneration of the basal nuclei of Meynert, which control central cholinergic innervation.

Genetic
About 10% of Alzheimer’s patients report other affected family members. There is Conflicting data from molecular genetics marker on 21 has been claimed and challenged

Microtubule, and other Cellular Damage Hypotheses

Aluminum
most popular environmental candidate
seems to be associated with senile plaques

Glutamatergic
degeneration of glutamatergic nerve terminals.

Dementia accounts for at least ½ of all nursing home beds.

Financial impact: present cost is estimated to be around 12 billion dollars.
Estimated to be 30 billion by 2030.

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Percent of Dementias
Alzheimer’s 50%
Mixed 15-20%
Vascular 17-29%
Pick’s 13-16%
Alcoholic Dementia 7%
**Philothermal**
Migration of white blood cells towards warmer temperatures impaired.

**Autoimmune**
Abnormal proteins (amyloid, for example).

**Infectious Agent**
Shown in other dementias (Creutzfeldt-Jakob, kuru, for example).
None identified, despite numerous attempts

**Head-Injury Hypothesis**
Many patients with Alzheimer's have had history of head injury.

**Blood-Flow Hypothesis**
Decreased blood flow and decreased oxygen consumption in Alzheimer's patients demonstrated on PET and SPECT. Not clear if this is a cause or effect of disease.

**Other**
Minerals, toxins, alcohol, drugs

**Vascular Dementia**
Can be due to a variety of vascular insults:
Large-vessel occlusion, usually due to cerebrovascular accidents
Small vessel occlusions, including multiple lacunar infarcts
Sclerosis of the recurrent arteries penetrating subcortical white matter from the cortex, probably due to chronic hypertension.
Border-zone infarctions, resulting from episodes of ischemia and/or hypotension.

**Pick's Disease**
Pathology: preferential degeneration of the frontal and anterior lobes
Pick bodies: ballooning of nerve cells with inclusions stained by silver compounds.

**Parkinson's Disease**
Destruction of dopaminergic cells originating from the substantia nigra in the midbrain.

**Huntington's Disease**
Hypometabolism, and then degeneration of the caudate nucleus
Autosomal dominant transmission with high penetrance
Gene localized to chromosome 4

**Lewy bodies**: found in some Parkinson's dementias. They occur in the cytoplasm of the remaining nigral neurons, and likely represent an early marker for neuronal
Premorbid determination of risk is available

**CREUTZFELDT-JAKOB DISEASE**
Spongiform Encephalopathy
multiple extracellular vacuoles seen microscopically in brain tissue.
Usually due to direct brain tissue inoculation of a unique proteinaceous material ("prion")
ex. Recipients of human growth hormone, which is harvested from cadavers, corneal transplant recipients.
May be genetically transmitted (rare)

**Diagnosis**

**ALZHEIMER'S**

Ultimately a pathological diagnoses, made on the observation of the (above) pathological findings.
Clinical assessments
Look for course typical of Alzheimer's (see below)
Accuracy can reach 80-90% if standard criteria (such as that in the DSM) as used
Typical Diagnostic Work up for Alzheimer's
Screening tests e.g. Mini-Mental State Exam
Neuropsychological Assessment
Tests to rule out other causes of cognitive decline (see Delirium section)

**VASCULAR DEMENTIA**

Look for evidence of sudden changes ("step-wise progression"), patchy deficits (very good at some things, while very bad at others, in a manner atypical of Alzheimer's).

**DSM-IV**
Same as Alzheimer's, with addition of focal neurological signs and symptoms or laboratory evidence indicative of cerebrovascular disease that are judged to be etiologically related to the disturbance.
focal signs: exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity

**Diagnostic criteria for Dementia of the Alzheimer's Type.**

1. Has to have Memory Impairment, and
one (or more) of the following cognitive disturbances:
aphasia
apraxia
impaired motor performance despite intact motor function
agnosia
failure to recognize or identify objects despite intact sensory function
disturbance in executive functioning e.g. planning, organizing,
laboratory evidence: multiple infarctions involving cortex and underlying white matter

**OTHER DEMENTIAS**

**Pick’s Disease**
characterized by signs of frontal lobe disease
personality change, usually disinhibition, and socially inappropriate behavior
personality change usually preceded memory and other cognitive problems
Functional brain imaging (Ex. PET, SPECT) often helpful in localizing the frontal hypometabolism.

**Parkinson’s Disease**
Characterized by typical symptoms of Parkinson’s disease
A Subcortical dementia

**Huntington’s**
triad of *dementia, psychosis and choreiform movements*
Dementia symptoms
personality changes
judgement deficits
but relative preservation of other cognitive functions

**Creutzfeldt-Jakob Disease**
Global dementia, usually with marked confusion
Generalized myoclonus, with exaggerated startle response
EEG shows characteristic periodic discharges

**HIV Dementia**
usually a subcortical type dementia
correlates with degree of HIV disease
be careful to rule out opportunistic infections, and other treatable causes of cognitive change

**Important Differential Diagnoses**

**Benign Senescent Forgetfulness**
Same as stage 2 of Alzheimer’s (see below) but doesn’t progress.

**Mild Cognitive Dysfunction**
Early cognitive deficits, not sufficient to cause significant dysfunction (therefore, not
A dementia). May or may not progress to dementia.

**Delirium**

**Depression**

Depression can cause cognitive deficits, often through the patients lack of motivation and tendency to overestimate deficits.

- may answer "I don't know" to most cognitive questions
- course of cognitive deficits tend to mirror course of the mood disorder
- should therefore improve with treatment

Term pseudodementia often used to describe cognitive deficits caused by depression, that are reversible with treatment with the depression.

Probably a misnomer

In actuality, depression and progressive dementia are probably often comorbid, and cognitive deficits often persist beyond resolution of the depression.

**Other Psychiatric Illnesses**

**Amnesia**

- only memory, not other cognitive functions affected
- often progresses to a dementia

**Malingering**

- most malingeringers are not good at replicating neuropsychological deficits typical of true dementias.
Common Comorbid Disorders

**DEPRESSION**

**ANXIETY**

**PSYCHOsis**

See corresponding discussions for each disorder

Typical course and prognosis of Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Stage of Cognitive Decline</th>
<th>Forgets</th>
<th>Remembers</th>
<th>Functioning</th>
<th>Behavior</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: None</td>
<td>not significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Very Mild</td>
<td>aware of some forgetfulness: names, losing items</td>
<td>most important things</td>
<td>normal</td>
<td>normal</td>
<td>appropriate concern</td>
</tr>
<tr>
<td>3: Mild</td>
<td>may remember little of what they read</td>
<td>most important things</td>
<td>coworkers becoming aware of poor performance</td>
<td></td>
<td>Anxiety, Denial</td>
</tr>
<tr>
<td>4: Moderate</td>
<td>Obvious memory deficits, including recent events. Concentration problems</td>
<td>oriented to time, recognizes familiar people and places</td>
<td>Trouble traveling alone or handling finances</td>
<td>Withdrawal from challenging situations</td>
<td>Denial</td>
</tr>
<tr>
<td>5: Moderately Severe</td>
<td>address, telephone number, familiar people, disoriented to time or place</td>
<td>own name, spouse and children</td>
<td>Cannot survive without assistance, cannot clothe self. Can eat and toilet</td>
<td></td>
<td>May be personality and emotional changes</td>
</tr>
<tr>
<td>7: Very Severe</td>
<td>Cannot communicate</td>
<td></td>
<td>Incontinent, needs assistance with all functions, may be unable to walk</td>
<td></td>
<td>agitation</td>
</tr>
</tbody>
</table>
**Vascular Dementia**
Varies. Usually progresses in step-wise progression.

**Pick's**
Progresses.
Personality changes early
Then cognitive disturbance
Motor disturbances occur late

Parkinson's
Dementia may improve with treatment of antiparkinsonians's. But the same treatment can also make the patient psychotic (think about why).

**Huntington's**
Insidious onset
Suicide and other psychiatric morbidity common

**Creutzfeldt-Jakob**
Rapidly progresses.

**Treatment**
Treat all treatable causes
but probably only < 10% of dementias are reversible

**Pharmacological**
Treating Alzheimer's

No definitive treatment, a lot of interesting ongoing research

Anticholinesterase Inhibitors restores lost Ach
only drugs approved for Alzheimer's

<table>
<thead>
<tr>
<th>Potentially treatable Causes of Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Drugs and Alcohol</td>
</tr>
<tr>
<td>- Tumors</td>
</tr>
<tr>
<td>- Nutritional: B12, folate</td>
</tr>
<tr>
<td>- Infections: Syphilis, abscess, encephalitis</td>
</tr>
<tr>
<td>- metabolic</td>
</tr>
<tr>
<td>- electrolytes</td>
</tr>
<tr>
<td>- hepatic</td>
</tr>
<tr>
<td>- renal</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
</tr>
<tr>
<td>- lupus</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
</tr>
<tr>
<td>- thyroid</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
</tr>
<tr>
<td>- subdural</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
</tr>
<tr>
<td>- Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
</tr>
<tr>
<td>- Depression</td>
</tr>
</tbody>
</table>
### Drugs Approved for Alzheimer's Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>tacrine (Cognex)</td>
<td>1993</td>
<td>cholinesterase inhibitor (CI)</td>
<td>nausea, vomiting, loss of appetite, and increased frequency of bowel movements (also liver effects in tacrine)</td>
</tr>
<tr>
<td>donepezil (Aricept)</td>
<td>1996</td>
<td>CI</td>
<td></td>
</tr>
<tr>
<td>rivastigmine (Exelon)</td>
<td>2000</td>
<td>CI</td>
<td></td>
</tr>
<tr>
<td>galantamine (Reminyl)</td>
<td>2001</td>
<td>CI and ACh stimulation</td>
<td></td>
</tr>
</tbody>
</table>

### Others Treatments

**Antioxidants**
free radicals produced through oxidation may be produced by beta-amyloid (a major component of the senile plaques)
antioxidants prevent or lessen free radical production
some interesting preliminary studies.
Czech researchers gave the antioxidant drug selegiline to 173 people with mild to moderate Alzheimer's disease. After six months, their memory improved significantly.
In another study, selegiline enhanced the benefits of tacrine

**Non Steroidals**
Some years ago, researchers noticed that people with severe arthritis have strikingly low rates of Alzheimer's disease.
More recently, Japanese researchers noted a similar unusually low rate of Alzheimer's disease in people being treated for leprosy.
Treatment of both leprosy and arthritis involves large doses of non-steroidal anti-inflammatory drugs (NSAIDS).
Meanwhile, researchers discovered that inflammation of brain tissue plays a key role in the development of neurofibrillary tangles and beta-amyloid plaques, the anatomical hallmarks of Alzheimer's disease.
These observations strongly suggested that NSAIDS might prevent, or at least delay, Alzheimer's disease, or help treat it.
Several studies have corroborated this speculation.
Estrogen
Several studies show that women who take estrogen after menopause have an unexpectedly low incidence of Alzheimer's disease.
Among women with Alzheimer's, those taking estrogen suffer less severe symptoms and slower mental deterioration.
Animal studies show that estrogen improves blood circulation through the brain, and stimulates nerve cell growth in areas of the brain affected by Alzheimer's.

Ampakines
new class of drugs that improve memory.
increase levels of AMPA-glutamate.
improved memory in animal studies.
Only human studies done in young adults with normal brain function. Showed improvement in memory.

Calcium Channel Blockers
As nerve cells die, they lose the ability to regulate the flow of calcium across their cell membranes. Some researchers speculate that calcium channel blockers, drugs that effect this minerals flow in and out of cells, may prolong nerve cell life.

Nerve Growth Factor
This hormone stimulates the growth of the nerve cells that release ACh.
Some researchers believe that by introducing nerve growth factor--or a similar compound--into the brains of people with early Alzheimer's, they may be able to slow or reverse cognitive deterioration.
Unfortunately, nerve growth factor does not cross the blood-brain barrier, so the hormone cannot be given orally or by injection.

Treating Symptoms Associated with the Disease
Similar reasoning to section under delirium.

Psychosocial Treatments
Attention to the care givers
find local support (ex. Alzheimer's association)
encourage family to keep up with activities
encourage family to educate themselves
good book: the 36 hour day.
Education for family
management
structured environment at home
regular scheduling
attention to their own lives
avoid confrontation
distraction best tactic when patient wants to do something they can't (drive, leave)

*TREAT COMPLICATIONS OF ILLNESS*

ex. Incontinence--look for urinary tract infections