Alzheimer's Dementia

History of Presenting Illness:
To qualify as demented, you must →

Differential Diagnoses
- Aphasia
- Cortical Basal Ganglionic Degeneration
- Dementia in Motor Neuron Disease
- Dementia with Lewy Bodies
- Frontal and Temporal Lobe Dementia
- Lyme Disease
- Multiinfarct Dementia
- Neuropsychilis
- Parkinson Disease
- Parkinson-Plus Syndromes
- Prion-Related Diseases
- Thyroid Disease
- Wilson Disease

Findings on History
Mainly interested in the above criteria, thus:
- determine progression (CHRONIC)
- determine degree of impairment
- personality change?
- Inappropriate behaviours?
- LATER CHANGES:
  - apathy,
  - decreased speech output,
  - failure to recognize family members,
  - incontinence.
- RULE OUT DIFFERENTIALS: diagnosis is by exclusion

Findings on Examination
- LISTEN TO THE LUNGS AND HEART! (These patients die of pneumonia and CHF)
  MMSE score of 24 or lower? = DEMENTED!
  Standard rate of decline is ~ 3 points every 6 months
  LOOK FOR GLOVE AND STOCKING SENSORY LOSS
  (could it all stem from B12/folate deficiency?)
  LOOK FOR FOCAL NEURO SIGNS
  (could it all stem from a massive temporal lobe tumour?)
  LOOK FOR ANAEMIC PALLOR
  (could it all stem from cerebral hypoxia?)
  LOOK FOR JAUNDICE (hepatic encephalopathy?)
  LOOK FOR ATRIAL FIBRILLATION (multiinfarct dementia?)
  LOOK FOR CLAUDICATION + Hypertensive Retinopathy

Evaluating delirium: Delirium is the impairment of attention.
It is tested by repetition of digits, or spelling “world” backwards.
Do what you like - the patient will have an INCOMPLETE MEMORY of these episodes
Cognitive/behavioural deficits: due in part to the deficit in attention.
...paranoia, aggression, PERSEVERATION, persecutory delusions
Acute/subacute time course: onset is typically over hours or days.
Fluctuations in the clinical state: frequently worse at night (sun-downing).
UNSTABLE VITAL SIGNS, due to autonomic involvement

PROGRESSIVE CHANGES:
MEMORY IMPAIRMENT AND...
Either
- Aphasia
- Apraxia
- Agnosia
- Loss of executive function
  eg. planning, organizing, sequencing, abstracting
- NOT RESULTING FROM
Delirium or a Psychiatric or Neurological disease
  *Early Onset: if onset is at age 65 years or below

commonest cause of dementia is Alzheimer’s disease = 60-80 % of
The next commonest is vascular dementia, = 10-20%

Findings which exclude Alzheimer's

Findings | Explanation
--- | ---
Sudden onset of dementia | Consider systemic disease, drug effect, cerebrovascular disease, infection, or tumor
Normal memory | Consider psychiatric disease, cerebrovascular disease, or early frontal lobe dementia
Plateaus in course | Alzheimer's disease is usually relentlessly progressive; consider stroke, amnestic syndrome
Depression | Consider pseudodementia secondary to depression
Personality change | If personality change is an early sign with minor memory loss, consider frontal lobe dementia
Seizures | Uncommon in early Alzheimer's disease, but do occur in late Alzheimer's disease; consider stroke, mass lesions

MINI MENTAL STATE EXAM = 30 points

Orientation (10 points)
Year, Season, Date, Day of week, and Month
State, County, Town or City
Hospital or clinic, Floor
Registration (3 points)
Name three objects: Apple, Table, Penny
Each one spoken distinctly and with brief pause
Patient repeats all three (one point for each)
Repeat process until all three objects learned
Record number of trials needed to learn all 3 objects
Attention and Calculation (5 points)
Spell WORLD backwards: DLROW
Points given up to first misplaced letter
Example: DLORW scored as 2 points only
Recall (3 points)
Recite the 3 objects memorized in Registration above
Language (9 points)
Patient names two objects when they are displayed
Example: Pencil and Watch (1 point each)
Repeat a sentence: ‘No ifs ands or buts’
Follow three stage command
Take a paper in your right hand
Fold it in half
Put it on the floor
Read and obey the following
Close your eyes
Write a sentence
Copy the design (picture of 2 overlapped pentagons)
**Tests and Investigations**
- **B12, folate, thiamine levels** (vitamin deficiency)
- **Blood glucose** (hypoglycemia)
- **Complete blood count** (anemia)
- **Drug screen** (drug toxicity)
- **Electrolytes** (hypercalcemia, hypermagnesemia, hypernatremia, uraemia)
- **Liver function** (liver disease, hepatic encephalopathy)
- **Lumbar puncture** (normal-pressure hydrocephalus, encephalitis, meningitis)
- **Thyroid function** (hypothyroidism)
- **VDRLT** (syphilis and HIV infection)

**IMAGING STUDIES** eg. CT and MRI: needed to exclude anatomical brain lesions eg. tumour. OTHERWISE on CT/MRI all you will see is **DILATED VENTRICLES and WIDENED SULCI**

**How is this diagnosis made?**

⇒ in AUTOPSY

Alzheimers is diagnosed by exclusion of everything else, until a brain biopsy is performed: THEN characteristic degenerative changes are witnessed

**Management of dementia:**

**MILD**
- Train the patient to help with their ADLS
- Treat their anxiety, depression, social phobia
- Refer them to social services eg. meals on wheels, community nursing etc.
- At this stage it is wise to address issues of will-making and enduring guardianship

**MODERATE**
- In-house assessment: are they able to continue living where they currently live?
- Informal support: engage neighbours, family etc.
- Formal support eg. nursing if they live alone

**SEVERE**
- Time to cart them off to a home.
- Residential care with help eating, dressing, hygiene
- This improves continence and nutrition
- Review their comorbidities (is it time to take them off some of their drugs, or put them on more)
- Socialize them to improve mental state (happy demented inmate = happier care-giver)

**“RAGING”**
- Uncommon, because most commonly the end-stage is APATHY and DEPRESSION
- EARLY FORM: depressed anxiety,
- MIDDLE FORM: vivid hallucinations and delusions
- AGGRESSION IS RARELY SPONTANEOUS! The staff usually deserve it

THUS: do not jump directly to the major sedatives and neuroleptics.

EDUCATE THE CARE-GIVERS AND MODIFY THEIR BEHAVIOUR

**TERMINAL DEMENTIA:**

⇒ DEATH from:
- Pressure sores, contracture (muscle shortening),
- Infections eg. pneumonia, dehydration, malnutrition

**PREVENTION OF DEMENTIA:**
- Avoid head injury!
- Don’t drink Alcohol or smoke!
- Control diabetes and cholesterol!
- Control atrial fibrillation!
- Drink Coffee!!

**WHO WILL CARE FOR THE CARE-GIVER?**
- Proven: improved care-giver mental health ⇒ improved QOL of demented patient
- !! BETTER and FEWER SYMPTOMS !!

**DEATH from:**

**ALZHEIMERS DRUGS**

**SYMPTOM CONTROL**
- Cholinergics, eg precursors (choline, lecithine) ⇒ weak long term effects
- CHOLINESETHERASE INHIBITORS: like neurotoxin Sarin: ⇒ Donepezil is the best one: dose = once per day (hard to forget even for a demented patient)

**FOR ACUTE EXACERBATIONS**
- ANXIOLYTICS (but NOT BENZO-based)
- NEUROLEPTICS in low doses Eg. olanzepine + haloperidol
- ANTIDEPRESSANTS or MOOD STABILISERS Eg. prozak or lithium
Management Of acute delirium:
Neuroleptics if you absolutely have to. **NO BENZOS!** → will make it much worse

**Prognosis**

The lifetime risk of developing Alzheimer's == 1:4
14% of individuals older than 65 years have AD
40% in individuals older than 80 years have AD

WOMEN ARE MORE AT RISK.

RISK DECREASES AFTER YOU REACH 90-100 y.o (good genes!)

**Epidemiology**

**RISK FACTORS FOR DEMENTIA**

A. **Age**
   1. Risk increases with age over 65 years

B. **Apo E4 Allele**
   1. Confers 8% risk if two allelles

C. **Family History of Alzheimer's Disease**

D. **FAD gene**

E. **Female gender**

F. **Low education**

G. **Head Trauma**

H. **Myocardial Infarction**

I. **Combined CV factors in middle age (odds ratio 3.5)**
   1. Hyperlipidemia
   2. Hypertension (increased systolic Blood Pressure)

**RISK FACTORS FOR DELIRIUM**

J. **Age over 60 years**

K. **Drug or alcohol addiction and withdrawal**

L. **Prior brain injury (vascular or traumatic injury)**

M. **Hearing Loss or decreased Visual Acuity**

N. **Insomnia or other sleep deprivation**

O. **Polypharmacy**

P. **Hospitalization or post-surgery**

Q. **Multiple comorbid conditions**

R. **Poor nutritional status**

S. **Hepatic failure**

T. **Chronic Renal Failure**

U. **Poor nutritional status**

- 3% of 65 – 74 year olds
- 20% of 75-84
- 45% of 85+
... are DEMENTED

**Pathophysiology : Age-associated brain changes:**

1. **Brain Atrophy:** decrease in size and weight (Male brains are normally 100g heavier)
   !! **SECULAR ATROPHY** !! is a normal difference: people in the beginning of the 20th century were born WITH SMALLER BRAINS therefore comparison is slightly off.

2. **Neurofibrillary tangles**
   → discussed below → see mechanism

3. **Neuronal Loss**
   → controversial - may not exist

4. **Cognitive Decline**
   → its no secret: old people have poor memories.
   There is a **LONG PRE-CLINICAL PERIOD** in Alzheimer's: steady decline with stable deficits.
**Risk Factors:**
- Advanced age
- High homocysteine
- Diabetes
- Down Syndrome

**Missense mutations in:**
- Amyloid Precursor Protein (APP)
- Pre-senilin-1 (a.k.a. gamma-secretase)
- Pre-senilin 2

**APP = transmembrane protein**

**TWO PATHS OF PROTEOLYSIS**

**Alpha-Secretase**
- Normal

**Gamma-Secretase**
- Abnormal

**DODGY INSOLUBLE AMYLOID PROTEIN**
- “A- (beta)-42- Peptide” collects in the ECF in the brain forms the characteristic early changes: PRE-AMYLOID DIFFUSE PLAQUES (perivascular collections of the pre-amyloid)

**AGGREGATIONS FORM:**
- “Amyloid Neuritic Plaques”
  - collections of amyloid in the neuritic processes
  - these UNDERGO AN INFLAMMATORY CHANGE

**NEURONAL LOSS AND DYSFUNCTION**

**ACETYLCHOLERGIC CELLS** in the BASAL FOREBRAIN are the first to go:
- Alertness
- Awakeness
- Short-term Memory

Next to fall:
- **ENTORHINAL CORTEX**
  - Forgetting episodic events
- **HIPPOCAMPUS**
  - Unable to consolidate STM → LTM

Then the bell tolls for:
- **TEMPORAL + PARIETO-OCCIPITAL REGIONS**
  - Aphasia, apraxia, agnosia
- **MED. FRONTAL + LIMBIC REGIONS** (! Amygdala!)
  - Social withdrawal, no enthusiasm,
  - Loss of insight, outbursts of anger

**AGGREGATES ARE HYDROPHOBIC**
- Hence insoluble, duh…

**HENCE:** they disrupt normal phospholipid bi-layer function and THUS DISTURB IONIC HOMEOSTASIS

**PARTICULARLY Ca++ !!!**

Excess Ca++ activates protein kinases, which means an increased rate of phosphorylation of TAU PROTEIN (a normal cytoskeleton component of microtubules)

**HYPERPHOSPHORYLATED TAU** forms paired helical filaments and organises into NEUROFIBRILLARY TANGLES

And disorganised axonal architecture = ANOTHER CHARACTERISTIC AUTOPSY FINDING

**DECREASED BRAIN VOLUME**
- plus
- **INCREASED VENTRICLE VOLUME** = Normal Pressure Hydrocephalus = YET ANOTHER CHARACTERISTIC AUTOPSY FINDING

**Mitochondrial lysis and thus APOPTOSIS**

**Oxidative injury**

**Acetylcholergic cells** in the BASAL FOREBRAIN are the first to go:
- Alertness
- Awakeness
- Short-term Memory

Next to fall:
- **ENTORHINAL CORTEX**
  - Forgetting episodic events
- **HIPPOCAMPUS**
  - Unable to consolidate STM → LTM

Then the bell tolls for:
- **TEMPORAL + PARIETO-OCCIPITAL REGIONS**
  - Aphasia, apraxia, agnosia
- **MED. FRONTAL + LIMBIC REGIONS** (! Amygdala!)
  - Social withdrawal, no enthusiasm,
  - Loss of insight, outbursts of anger
Anatomy and Physiology of Memory (a’la Mitrofanis)

Thing to know:
MEMORY IS NOT AN ACTUAL BRAIN PROPERTY
More like something we infer from behaviour

CATEGORIES OF MEMORY:

PROCEDURAL vs DECLARATIVE:
PROCEDURAL is unconscious, automated eg.
remembering how to write, what language to speak
→ VIA BASAL GANGLIA + CEREBELLUM (climbing fibres of cerebellum)
  + Red nucleus and Olive of medulla

DECLARATIVE MEMORY is the conscious variety
= its facts and events
separated into SHORT and LONG TERM
according to no real criteria, eg
Short Term Memory means about 5 minutes

SHORT TERM MEMORY:
Based in the secondary cortex of each sense (i.e visual memories are all kept together for a while in the occipital lobe)
The Pre-Frontal Cortex pools these together; somehow the Basal Forebrain is involved in their storage and distribution (Acetylcholine cells with widespread connections)

LONG TERM MEMORY: permanent storage with HUGE capacity
Mediated by the MIGHTY HIPPOCAMPUS
→ IT DOES EVERYTHING
Long term memories are stored in the NEOCORTEX, vaguely associated with the sensory area of their origin
* AMYGDALA is involved in the emotional tagging of memories

ATTENTION and DELIRIUM

Delirium is the impairment of attention.
Tested by repetition of digits, or spelling “world” backwards

Attention comes in 2 flavours: GLOBAL and SPECIFIC

GLOBAL ATTENTION:
is stimulated by all systems;
works via the Brainstem Reticular Formation → via Thalamus → to the cortex
runs on Acetylcholine;
Ach from basal forebrain WAKES US UP
Serotonin determines HOW AWAKE and ALERT

SPECIFIC ATTENTION
Unimodal, i.e ONE THING AT A TIME
The Components:
  Parietal cortex (filters relevant from irrelevant)
  Sup. Colliculus of Midbrain (motor reflex avoidance of incoming missiles)
  Pulvinar Thalamus, (Pulvinar prioritises eye movements upon orders from sup. colliculus)

How attention is gathered on one target:
The THalamocortical PATHWAY (of thalamic reticular nucleus → cortex) does this:
  It AMPLIFIES ONE INPUT and
  INHIBITS ITS SURROUNDINGS
  THUS, attention is focussed.

USEFUL RULE OF THUMB:
SEDATION = REDUCES MEMORY-MAKING
AROUSAL = INCREASES MEMORY-MAKING