DEMENTIA

DEFINITION

- Dementia is derived from Latin *de mens* meaning "out of mind"
- It is not a diagnosis by itself but refers to a clinical state
- Mild cognitive impairment – distinguished from dementia by lack of functional impairment

CLASSIFICATION

- **Cortical dementia**: causes gross personality changes
  - **Fronto-temporal**
    - Pick's disease
    - Semantic dementia
    - Progressive Non-fluent Aphasia (PNFA)
    - Motor neurone disease
    - Normal pressure hydrocephalus (NPH)
  - **Posterior-parietal:** featured by early memory loss and focal cognitive deficits
    - Alzheimer's disease
- **Sub-cortical dementias**: characterised by gross psychomotor slowing, abnormal movements, low mood, mild amnesia and apathetic personality
  - Parkinson's disease dementia
  - Huntington's disease,
  - HIV associated dementia,
  - Binswanger's disease and
  - Wilson's disease

CONT.

- **Cortical-subcortical dementia:**
  - Lewy Body dementia: both cortical and sub-cortical features are present.

- **Multifocal dementias:**
  - Creutzfeldt-Jacob disease: involves cerebellum and subcortical structures.

PREVALENCE

- Alzheimer's Dementia 55%
- Vascular dementia 20%
- Dementia with Lewy body 15%
- Fronto-temporal dementia 5%
- Other causes 5%

ALZHEIMER'S DEMENTIA

- Commonest type
- Prevalence:
  - 5% at 65 years
  - 20% at 80years

- Predisposing factors:
  - **Proven**: Old age, Down's syndrome, Apo-lipoprotein E genotype
  - **Likely**: female sex, head injury, postmenopausal oestrogen decline
  - **Possible**: family history of Down's syndrome, family history of Parkinson's and vascular factors

GENETICS

- Genetics: early onset form have an autosomal dominant mode of inheritance.
  - Mutations that increase the risk of AD have been identified in 3 genes:
    - 2 that code for constituents of the secretase enzyme that cleaves Aβ from APP:
      - **Presenilin 2 gene** (chromosome 1)
      - **Presenilin 1 gene** (chromosome 14)
    - **APP gene** (chromosome 21, Beta-amyloid precursor protein)

- Inheritance of late-onset form is multifactorial and polygenic.
  - The **ApoE gene** contributes most to the genetic component
  - There are 3 common ApoE alleles (E2, E3, E4); the E4 allele particularly if homozygous indicates increased likelihood of early onset.

RISK FACTORS

- Increasing age
- Family history (RR is 3.5 in first degree relatives)
- Down's syndrome
- Apo-lipoprotein E genotype
- Other possible risk factors (where evidence is not so clear) include:
  - Head injury (NFTs found in dementia pugilistica, but some studies have failed to find an association.
    - Dementia pugilistica: type of chronic traumatic encephalopathy; neurodegenerative disease with features of dementia; May affect amateur or professional boxers; It is caused by repeated concussive and sub-concussive blows to the head.
  - Aluminium (one study showed association with level of aluminium in drinking water)

CONT.

- Organic solvents
- Smoking (although some studies show it is protective!)
- Hypothyroidism
- Depression
- Family history of Down's syndrome
- Family history of Parkinson's disease
- Increasing maternal and paternal age at time of birth
- Other conditions e.g. diabetes, infections, vascular dementia

PROTECTIVE FACTORS

- Hormone replacement therapy - not supported by studies
- Anti-inflammatory drugs
- Control of hypertension
- Fish consumption
- High pre-morbid verbal ability

AD: NEUROPATHOLOGY

- Macroscopically:
  - Diffuse atrophy with flattened/widened cortical sulci and enlarged cerebral ventricles.
  - **Neuronal loss** especially in the cortex and hippocampus
  - **Granulovacuolar degeneration** of the neurones
  - **Synaptic loss** in the cortex
- Pathognomonic microscopic findings are:
  - **Senile (Amyloid) plaques** containing a protein called **Aβ** that is cleaved from the **amyloid precursor protein (APP)**
  - **Neurofibrillary tangles (NFTs)** – Insoluble aggregates of hyper-phosphorylated tau protein (primary marker of AD)
- Amyloid plaques are also seen in:
  - Normal aging
  - Down's syndrome

CONT.

- NFT also occur in:
  - Down’s syndrome
  - Dementia pugilistica
  - Parkinson's disease
  - Normal aging
- NFT are commonly found in the:
  - Cortex
  - Hippocampus
  - Substantia nigra
  - Locus coeruleus
- Plaques and tangles correlate with the severity of the clinical picture in DAT

NEUROTRANSMITTERS

- Neurochemically, there are deficits in:
  - **Acetylcholine (hypoactive)**
    - Degeneration of cholinergic neurones in the nucleus basalis of Meynert leads to decreased Acetylcholine and choline acetyltransferase concentrations in the brain
  - **Noradrenaline (hypoactive)**
    - Decreased norepinephrine containing neurones in the locus coeruleus has been demonstrated
  - **Serotonin**
  - **Somatostatin**
  - **Corticotrophin**

STAGES OF AD PRESENTATION

- **Stage I**
  - Amnesia
  - Spatial disorientation
- **Stage II**
  - Personality disintegration
    - Aggression, psychosis, agitation, depression
  - Focal parietal signs
    - Dysphasia, Apraxia, Agnosia, Acalculia
  - Parkinsonism may occur
  - Hyper-orality (use the mouth to examine objects)
- **Stage III**
  - Neurovegetative changes with apathy (or akathisia)
  - Wasting, immobility, urinary incontinence
  - +/- seizures and spasticity
- Mean survival is 7 years from clinically (overt) onset

CLINICAL FEATURES OF AD

- Insidious onset
- The 4 As:
  - Amnesia (loss of recent memory)
  - Aphasia (speech changes)
  - Apraxia (difficulty in simple motor functions)
  - Agnosia (difficulty in recognising people and things)

- Behavioural and psychiatric symptoms of AD
  - Disorders of thought content
  - Disorders of perception
  - Disorders of affect
  - Behavioural disturbance
  - Personality change

PSYCHOTIC SYMPTOMS

- Delusions (15%)
  - Delusions are more common than hallucinations
- Auditory and visual hallucinations (10-15%)
  - These are common than other modalities
- Depression (20%)
- Psychosis (30 – 50%)
  - Psychotic symptoms are associated with rapid decline

PHYSICAL SYMPTOMS IN AD

- **Weight loss** and **weakness**, **stooped posture** and non specific or apraxic **abnormalities of gait**
- Progressive physical deterioration, often resulting in gross wasting, leading to **bronchopneumonia**, the commonest form of death
- Urinary incontinence - a late feature of AD
- Physical problems such as urinary incontinence, decreased mobility and balance problems are more commonly seen in people with vascular dementia than with AD.

DIAGNOSIS OF AD

- Full psychiatric history and informant history.
- Mode of onset, course of progression, pattern of cognitive impairment.
- Non-cognitive symptoms i.e. behavioural disturbance, wandering, aggression (catastrophic reaction).
- Presence of co-morbid depression.
- Mental state examination.
- Family history.
- Other diagnostic possibilities e.g. vascular, rule out possible organic causes.

INVESTIGATIONS

- Full blood count and ESR
- Blood glucose
- Vitamin B12 and folate
- Thyroid function tests (TFT)
- Urea and electrolytes
- Liver function tests
- Midstream urine sample (MSU)
- Chest X-ray
- Electrocardiogram (ECG)
- Electroencephalogram (EEG)
- Computed tomography (CT) scan

DIFFERENTIAL DIAGNOSIS

- Delirium
- Depression
- Psychotic disorders

MANAGEMENT

- History
- Collateral history
- Medical records
- Social worker reports
- Home visits
- Investigations

CONT.

- Diagnosis
- Psychological, behavioural
- Social
- Risk
- Biological
- Carers' health
- Legal aspects: advance directives, power of attorney, wills

NICE GUIDELINES ON ACHE INHIBITORS

- AD **must be diagnosed in a specialist clinic** by a specialist (psychiatrists, neurologists, physicians with a special interest in care of the elderly)
- **Carers' views** at baseline must be sort.
- The patient must have **moderate AD** ONLY (MMSE <Mini-Mental State Exam> between 10 and 20)
- Cognition (MMSE), global and behavioural functioning including ADLs should be assessed at baseline and every 6 months after commencing treatment. Carers' views should be sought.
- The **drug should be continued only while the patient's MMSE score is above 10** and their level of functioning and behavioural condition remains at a level where the drug is considered having a worthwhile effect.

ACHE INHIBITORS (INCREASE CNS ACH)

- **Donepezil** 5-10mg OD. Steady state reached in 14 days. Single dose (easier to take)
- **Rivastigmine** 3-6mg BD. Half-life 10 hours.
- **Galantamine** 8-12mg BD. Half-life 6 hours.
- **Memantine**, a NMDA receptor antagonist, may help moderate to severe AD. It is given at 10mg BD and it is considered to be neuroprotective and disease modifying
- **Cautions**
  - Creatinine increase
  - Epilepsy
  - Side effects:
    - GIT, Heart, Obstructive airways disease
    - Confusion, Headache, hallucinations, fatigue,
    - Rarer: Vomiting, anxiety, hypertonia. Cystitis, increased libido

OTHER MEDICATIONS

- **Anti-oxidants** such as gingko Biloba, Selegiline
- **Vitamin E** in the treatment of AD
- Medical treatment of behavioural and psychiatric disorders related to AD includes the use of **SSRIs and antipsychotics.**

ACHEI

- Improve cognition – measured by MMSE or subjective as seen by carers

PRACTICAL HELP

- Exclude treatable dementias like
  - B12 or folate deficiencies
  - Syphilis
  - HIV
- Treat concurrent illnesses as they worsen dementia
- Avoid sedatives and neuroleptics
- In most, dementia progresses

PSYCHOLOGICAL TREATMENTS

- Errorless learning
- External memory aids
- Cognitive stimulation therapy
- Behaviour modification
- Validation therapy
- Reminiscence therapy
- Memory training

OTHER TREATMENTS

- Targeting β-amyloid
  - Drugs preventing aggregation of β-amyloid.
  - Drugs to inhibit secretase by which β-amyloid is formed from APP.
  - Immunisation strategies.
- Other approaches include;
  - hormone replacement therapy
  - NSAIDs
  - Statins
  - Folate supplementation
  - Aroma therapy
- Other targets include tau and its hyper-phosphorylation.

Prognosis

- Downward progression
- Medications do not alter course of the disease
- Death from complications in 5 – 8 years

NON- ALZHEIMER TYPE DEMENTIA

INCLUDE:

- **Mild cognitive impairment**
- **Vascular dementia**
  - Binswanger's disease
  - CADASIL (**C**erebral **A**utosomal **D**ominant **A**rteriopathy with **S**ubcortical **I**nfarcts and **L**eukoencephalopathy)
- **Dementia with Lewy Bodies**
- **Fronto-temporal dementia**
  - Pick's disease
  - Progressive non-fluent aphasia (PNFA)
  - Semantic dementia
  - Motor neuron disease
  - Progressive supra-nuclear palsy (PSP)
- **Prion disease**
  - Kuru
  - Creutzfeldt Jacob disease
  - Fatal Familial Insomnia
  - Gerstmann Straussler syndrome

Potentially reversible causes

- **Intracranial causes**
  - Normal Pressure Hydrocephalus (NPH)
    - May be idiopathic or due to SAH, head injury or meningitis.
    - Presentation: Marked mental slowing, apathy, wide-based gait, urinary incontinence
    - Ventriculoatrial shunting →frequent complications
  - Subdural haematoma (SDH)
  - Cerebral tumours
  - GPI (General Paresis of the Insane) – Caused by chronic meningoencephalitis that leads to cerebral atrophy in late-stage syphilis.
- **Systemic disorders**
  - Alcoholism
  - Anoxia
  - Hypoglycaemia
  - Myxoedema
  - Vitamin deficiencies
  - Drug and chemical poisoning
  - Pseudo-dementia
  - Renal and hepatic disease

Mild Cognitive Impairment (MCI)

- Many different terms
- Main difference from Alzheimer's disease is **lack of functional impairment**
- A significant proportion develop Alzheimer's disease on follow up (10-15% per year)
- Cholinesterase inhibitors are not recommended presently (Cochrane on Donepezil, 2 RCTs, mixed results)
- Improvements in physical health and mental stimulation may help

Vascular Dementia

- Imprecise diagnostic group of disorders
- Range from single stroke to multi-infarcts to ischemia
- Overlap with Alzheimer's disease in older people (mixed)
- In addition there are:
  - Binswanger's disease
  - CADASIL
- Prevalence: more common in
  - Males
  - Eastern countries

Vascular dementia - Etiology

- Vascular risk factors
  - Hypertension, hyperlipidemia, diabetes, obesity, lack of exercise
  - Common after a stoke (up to 30% at 6 months)
  - IHD, atrial fibrillation
  - Alcohol, Smoking
- ApoE → small increase in risk compared to AD

Pathology - VD

- Blessed in the 1960s described **critical volumes of infarct to cause dementia**
- VD is associated with more patchy cognitive impairment than AD; focal neurological symptoms or signs appear in a 'step-wise' rather than a continuous deterioration.
- Pathologically, there is at least one area of cortical infarction
- Still no internationally agreed pathological criteria
- Problem is how to correlate size and position of infarcts with cognitive impairment
- NINCDS-AIREN clinical criteria have: sensitivity 43%, specificity 95%

HACHINSKI ISCHAEMIC SCALE (1974)

- **2 points for:**
  - Abrupt onset
  - History of strokes
  - Focal neurological symptoms and signs
  - Fluctuating course
  - Atherosclerosis
- **1 point for:**
  - Stepwise deterioration
  - Nocturnal confusion
  - Relative preservation of personality
  - Depression
  - Somatic complaints
  - Emotional incontinence
  - History of hypertension

INVESTIGATIONS

- Same as Alzheimer's disease
- + Lipids, ECG
- MRI - White Matter Hyper-intensities (WMH)
- SPECT - irregular pattern

MANAGEMENT - VD

- Control vascular risk factors (especially blood pressure)
- Aspirin
- Cholinesterase inhibitors and Memantine have modest benefits
- No regulatory or NICE approval as yet

PROGNOSIS

- Slightly worse than Alzheimer's disease
- Depression is more common

BINSWANGER'S DISEASE/SUB-CORTICAL ARTERIOSCLEROTIC ENCEPHALOPATHY

- Slow intellectual decline
- Sub-cortical dementia, gait problems, dysphasia
- Imaging shows infarcts (lacunae), and extensive white matter changes in distribution of small vessels

CADASIL (CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY)

- **Rare**
- Mainly found in **continental Europe**
- Onset in **40s**
- Gene on **chromosome 19**

LEWY BODY DEMENTIA (LBD)

- **LBD** is an umbrella term for 2 related clinical diagnoses:
  - **Dementia with Lewy bodies**
    - People whose dementia occurs before or within 1 year of Parkinson's symptoms are diagnosed with LBD.
  - **Parkinson's disease dementia (PDD)**
    - People who have an existing diagnosis of Parkinson's for more than a year and later develop dementia are diagnosed with PDD
- **Lewy bodies** (cytoplasmic inclusions) & **Neurites** are found in the cerebral cortex and basal ganglia.
- Lies on a spectrum between Alzheimer's disease pathology and Parkinson's disease

Pathology - LBD

- Lewy bodies contain **alpha-synuclein**, a misfolded protein.
- Senile plaques may be present
- Deficits of acetylcholine and dopamine

CLINICAL FEATURES LBD

- **Central feature:**
  - Progressive Dementia – worse executive function and visual-spatial impairment, better verbal memory
- **Core features:**
  - Delirium – fluctuating cognition and alertness over minutes, hours or days.
  - Recurrent, vivid, visual hallucinations – involving humans or animals
  - Spontaneous parkinsonism – bradykinesia, rigidity and falls
- **Suggestive features:**
  - Severe sensitivity to antipsychotics (neuroleptic medication) → approx. 50%
  - REM sleep Behavior Disorder (RBD) – vivid dreams & motor activity
  - Low Dopamine transporter uptake in the brain's basal ganglia seen on SPECT and PET imaging scans
- **Supportive features:**
  - Repeated falls and syncope (fainting)
  - Transient, unexplained LOC
  - Autonomic dysfunction
  - Hallucinations of other senses, like tactile and auditory
  - Visuospatial abnormalities

OPERATIONAL CRITERIA FOR LBD

- Fluctuating cognitive impairment
- At least one of:
  - Visual (60-80%) or auditory hallucinations
  - Mild, spontaneous, extrapyramidal features
  - Repeated unexplained falls or transient clouding or loss of consciousness
  - Increased sensitivity to neuroleptics
- Persistent and often rapidly progressive course
- Exclusion of a physical cause of the syndrome
- Exclusion of vascular pathology

INVESTIGATIONS LBD

- As for Alzheimer's disease
- CT – no distinct picture
- MRI – relative preservation of hippocampus and medial temporal lobe compared to AD
- SPECT – occipital hypo-perfusion (not useful in ID)
- DaTSCAN: reduced uptake of isotope into the caudate nuclei
  - DaTSCAN is a radiopharmaceutical imaging agent that works by binding to dopamine transporters (DaT)

MANAGEMENT - LBD

- Make the correct diagnosis
- Education for patient and care-givers
- Attend general physical health
- Avoid antipsychotics

MEDICATIONS

- **Cholinesterase inhibitors** – may be helpful for visual hallucinations, but may make Parkinson symptoms worse

- **Clonazepam** – may help REM sleep disorder

- **L-DOPA** – less affective than for Parkinson's with dementia

PROGNOSIS

- May be worse than Alzheimer's disease
- Death hastened by antipsychotics
- Depression more common

FRONTO-TEMPORAL DEMENTIAS

- Include:
  - PNFA
  - Semantic dementia
  - MND
  - FTD
  - Corticobasal syndrome
  - PSP
  - Pick's disease
- First case identified by Pick in 1892
- But not until the 1990s was there a clear understanding
- Partly due to complex nosology
- They have a younger mean age of onset and account for up to 20% of early onset dementias.
- **Characteristics:**
  - Early personality changes
  - Relative intellectual sparing
  - Mainly affects frontal and anterior temporal lobes
- **Pathology:**
  - Heterogeneous
  - **Ubiquitin** or **tau** (positive) inclusions

FRONTOTEMPORAL DEMENTIA (FTD)

- Hallmark is a **change in social, interpersonal and emotional behavior**.

- Symptoms include:
  - Dis-inhibition
  - Inappropriate behavior,
  - Personality change,
  - Eating disorder,
  - Lack of insight,
  - Apathy,
  - Executive dysfunction

PATHOLOGY – PICKS DISEASE

- Atrophy – frontal and temporal lobes with sparing of posterior third of the superior temporal gyrus → **Knife-blade atrophy**

- Signs include:
  - Dementia
  - Aphasia

- Pick cells – ballooned neurons
- Tau
- Progranulin

GENETICS

- Up to 50% have a family history
- Mutations of tau progranulin account for 5% of FTD

PROGRESSIVE NON-FLUENT APHASIA (PNFA)

- Impaired language: speech is slow and hesitant, effortful with numerous errors
- Comprehension relatively spared but may be affected
- Normal memory, visuospatial function, behavior

Semantic dementia

- Hallmark is an anomia, fluent speech but a difficulty with the meaning of words
- e.g. unable to name a hammer, or to demonstrate its use
- Also behavioral abnormalities and obsessive-compulsive symptoms

FRONTOTEMPORAL DEMENTIA – MOTOR NEURONE DISEASE (MND)

- Overlap between the disorders

- 10-15% of people with FTD develop MND

PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

- Parkinsonism
- Axial rigidity
- Falling backwards
- Eye movement abnormalities
- Pseudobulbar syndrome (dysarthria, dysphagia)

INVESTIGATIONS - PSP

- Same as Alzheimer's disease
- MRI – atrophy of frontal lobes and insula
- SPECT – hypoperfusion in frontal lobes

MANAGEMENT - FTD

- Identification
- Education
- Pick support groups
- **SSRIs** – serotonergic deficits
- **ACHEIs** – not so helpful, may worsen restlessness

PRION DISEASES

- Prion protein may undergo mutation rendering it insoluble.

- Prions cause **Transmissible Spongiform Encephalopathies (TSEs)**
  - Kuru
  - Creutzfeldt Jacob disease
  - Fatal familial insomnia
  - Gerstmann Straussler syndrome

DEMENTIA IN CREUTZFELDT-JACOB DISEASE

- General criteria for dementia

- **Rapid progression** of the dementia

- One or more of the following neurological symptoms and signs:
  - Pyramidal symptoms
  - Extra-pyramidal symptoms
  - Cerebellar symptoms
  - Aphasia
  - Visual impairments

Conclusion

- The dementias reveal how the healthy brain works:
- MCI – Controversy over when impairment is dementia
- Alzheimer's dementia → Global impairment
- Vascular dementia → Covers the whole spectrum of cerebrovascular disease and cognition
- DLB → Sits on the interface between AD, delirium and Parkinson's disease
- FTD → Reveals how the frontal lobes govern personality and theory of mind