

# Familial Alzheimer's disease

## Familial Dementing Disorders

### Alzheimer and Parkinson

- Two common neurologic disorders
- May have common linkage
- Chronic and present with heavy societal burden with aging population
- There is light at the end of the tunnel due to biochemical advances
- Dementia is a common feature

### Dementia defined

DSM IV “The development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in the occupational or social functioning and must represent a decline from a previously higher level of functioning.”

### Dementia defined

- ICD 10 “A decline over at least 6 months in memory, deterioration in judgment and thinking, absence of clouding of consciousness, decline in emotional control or motivation or change in behaviour.”

### Histological features of Alzheimer

- Neuronal loss
- **NEURITIC “SENILE” PLAQUES**
- **NEUROFIBRILLARY TANGLES**
- Amyloid angiopathy
- Granulovacuolar degeneration
- Hirano bodies

### Neuritic plaques

- Central core of amyloid which is amorphous, extracellular, congophilic, PAS positive and argyrophilic
- Surrounded by microglia and reactive astrocytes
- Birefringent on cross polars with congo red with a Maltese cross appearance
- Originally described by Bellini 1889

### Neurofibrillary tangles (NFT)

- Originally described by Alzheimer 1906
- Appear as paired filaments on electron microscopy
- Intense argyrophilia
- Made up of phosphorylated  $\tau$  (tau) protein
- Extremely stable

Evidence of amyloid as main pathology

- $\beta$ -amyloid plaques are seen in ALL Alzheimer
  - 2. Mutations in several genes cause Familial Alzheimer have amyloid deposit
  - 3. Trisomy 21 (Down's) cause amyloid deposit
  - 4. Apo $\epsilon$ 4 *promote* amyloid aggregation
  - 5. A $\beta$  peptide is toxic to all cells
  - 6. Other sources of amyloid as transthyretin (familial polyneuropathy) damage tissues
- How is amyloid formed in the CNS?
- Origin is **Amyloid Precursor Protein (APP)**, a useful neuronal cell membrane protein; an isoform also seen in platelets
  - Degraded by kinases to form A $\beta$ 4
  - If it is acted by  $\alpha$ -secretase, no amyloid deposit; but if acted on by  $\beta$ -secretase and  $\gamma$ -secretase, amyloid is formed (A $\beta$ 42 and A $\beta$ 40) Cu/Zn promote amyloid formation.
  - Insulin promotes movement from intracellular to extracellular space

Down's syndrome

Trisomy in chromosome 21 leads to over-expression of APP and overload of A $\beta$  protein and degraded by secretase

Familial forms of Alzheimer

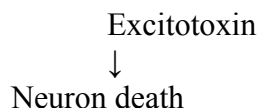
| Chromosome | Gene                          | Phenotype                                 |
|------------|-------------------------------|---|
| 21         | APP mutation                  | $\uparrow$ A $\beta$ 40                   |
| 19         | Apo $\epsilon$ 4 polymorphism | $\uparrow$ A $\beta$ plaque, blood vessel |
| 14         | Presenilin 1 mutation         | $\uparrow$ A $\beta$ 42                   |
| 1          | Presenilin 2 mutation         | $\uparrow$ A $\beta$ 42                   |

Precis

Inflammatory Cytokines

- TNF $\alpha$ , Interleukines

- COX  $\rightarrow$  Prostaglandins  $\rightarrow$  Glutamate



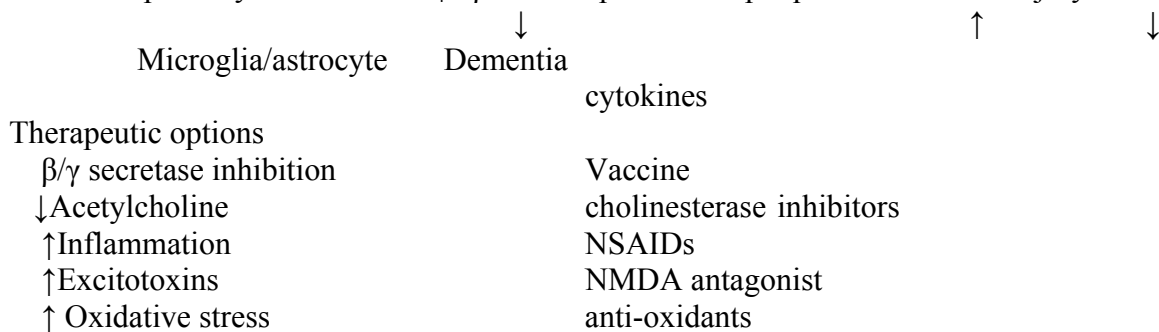
## Estrogen

- Ever controversial but estrogen may
  - block A $\beta$  peptide formation
  - $\uparrow$  growth nerve factor for memory
  - $\uparrow$  Acetylcholine and serotonin
  - open blood vessels
  - act as anti-oxidant

## Hypothetical pathogenesis of Familial Alzheimer

Missense mutation of APP, PS-1, PS-2 genes

$\rightarrow$  altered proteolysis of APP  $\rightarrow$   $\uparrow$  A $\beta$ 42  $\rightarrow$  deposition as plaques  $\rightarrow$  neuronal injury



## Available drugs

Anticholinesterase

Galantamine

Donezepil

Rivastigmine

NMDA antagonist

Memantine, Lamotrigine?

Antioxidants

Vitamin E

Selegeline

Lycopene

Anti-inflammatory

Ibuprofen, indomethacin, sulindac

Secretase inhibitors

Vaccine (A $\beta$ 42), clioquinol (Zn chelator)

Apo $\epsilon$  control

HMG-CoA reductase inhibitors

(statins)

## Sunrise drugs

- Phenserine – anti-AChE and anti-amyloid
- Amyloid inhibiting peptides (AIPs)
- Posiphen – anti-amyloid
- Tolserine – AChE inhibitor
- Phenethylnorcysmerine – anti-BChE

## Parkinson's disease

- Described by James Parkinson 1817

- Clinical triad
  - Tremor
  - Akinesia
  - Rigidity

Tremor

- Resting tremor
- Slow 6-12 Hz
- Pill rolling
- Hands, feet and lips
- Exacerbated by emotions

Akinesia

Blank, masked-like facies

Reptilian stare

Lack of spontaneity of movement volitional and emotional

Stooped posture

Rigidity

- Cog-wheel
- Plastic
- Affect nuchal, trunk, limbs
- Respiratory difficulties

Others

↑Salivation

Loss of postural control

Festinating gait

Myerson reflex

**Poor mentation** (either spontaneous or aggravated by drugs)

Freezing phenomenon

Diseases with Parkinson features

- Idiopathic Parkinson
- Post-encephalitic Parkinsonism
- Progressive supranuclear palsy
- Fronto-temporal dementias
- Parkinson dementia complex
- Diffuse Lewy body disease
- Multi-system atrophy (Shy-Drager syndrome)
- Strio-nigral degeneration
- Wilson's disease
- Drug induced (Anti-psychotic drugs)
- X-linked dystonia (Lubag of Panay)

Neuropathology

–Severe loss of dopaminergic neurons in substantia nigra

- Lewy bodies

#### Onset of Parkinson

Juvenile <35 years  
Early onset 35-50 years  
Late onset >50 years

#### Tauopathies

##### Frontotemporal dementias

- Frontotemporal dementia Parkinson 17
- Pick's disease
- Corticobasal degeneration
- Progressive supranuclear palsy

#### FRONTO-TEMPORAL DEMENTIA PARKINSON 17 (FTDP 17)

. Rare (?) form of dementia, a tauopathy  
Diagnosis based on  
Clinical Features  
Neuroimaging and autopsy  
Family History – autosomal dominant

#### FTDP 17 Clinical features

- Abnormal behavior
- Emotional symptoms
- Cognitive symptoms
- Neurological manifestations

#### FTDP 17 Clinical Features

- Onset between 40 – 60 y, death in 5 – 10 y
- Behavioral symptoms
  - hyper-oral – overeating
  - stereotype – e.g. clapping, hand rubbing
  - poor personal hygiene
  - hyperkinesia – wandering
  - impulsive acts – e.g. shoplifting

#### Emotional symptoms

- Apathy, indifference, lack of initiative (Abulia)

- Poor insight
- Emotional blunting – lack of warmth, sympathy
- Mood changes

#### FTPD 17 Cognitive symptoms

- Poor “executive function”
  - distractability and impersistence (poor concentration)
  - Mental rigidity – inflexibility poor adaptation
  - Poor planning and problem solving (poor abstract reasoning)
  - Poor financial judgment

#### FTDP 17 Neurological manifestations

. Movement dysfunction with strong Parkinsonian features, alien hand syndrome

. Seizures

#### FTDP 17 Neuroimaging

- ↓blood flow in anterior part of brain
- Atrophy of cerebral cortex

#### FTDP 17 Family history

- Strong Family history in first degree relatives – brothers and sisters, children
- Abnormal gene may arise de novo*

#### FTDP 17 autopsy

- irregular tau protein in frontal, temporal cortex
- neuronal loss
- extensive gliosis
- gene abnormality in chromosome 17
- MAPT (microtubule associated protein tau)