

## Dementia of Early Onset

- term initially introduced in 1894 by Binswanger
- later included in Kraepelin's classification
- now defined as onset of dementia before the age of 65
- Ron *et al.* (1979) followed up 51 patients after a diagnosis of presenile dementia - the original diagnosis was rejected in a third of cases

### Causes

1. Alzheimer's disease of early onset
2. Dementia of frontal lobe type
3. Vascular dementia
4. Alcoholic dementia
5. Normal pressure hydrocephalus
6. Dementia in other conditions :
  - a) Pick's disease
  - b) Parkinson's disease
  - c) Huntington's chorea
  - d) Prion diseases
  - e) HIV infection (AIDS dementia complex, ADC) :
    - i) found in 15 % of patients with advanced HIV disease

### Alzheimer's disease

#### Epidemiology

- F:M ratio is 2:1
- 10 % of population over 65 years and between 25 and 40 % over 85 years have Alzheimer's disease
- the condition generally lasts 7-15 years

#### Aetiology

1. *Trauma* :
  - a) is an independent risk factor but perhaps only in those with a genetic predisposition
2. *Genetic* :
  - a) a family history of Alzheimer's disease increases the risk of the disease four-fold
  - b) familial forms are inherited as an autosomal dominant trait
3. *Molecular genetics* :
  - a) mutations in the **chromosome 14** locus are responsible for most early-onset, familial Alzheimer's disease
  - b) the *apolipoprotein e gene* on **chromosome 19** has been implicated in late-onset Alzheimer's disease
    - i) the genotype  $\epsilon 4$ - $\epsilon 4$  confers a higher risk

- c) patients with trisomy of chromosome 21 (Down's syndrome) have a high risk of early-onset Alzheimer's disease - the gene for ***β-amyloid precursor protein*** is found on **chromosome 21**

### Pathology

1. diminution of the cortex and subcortical white matter volume, with dilatation of the cortical spaces and enlargement of the lateral ventricles
2. *Loss of cortical neurones* :
  - a) particularly in outer 3 layers of cortex, but all layers affected
  - b) hippocampus, parietal regions, and nucleus basalis of Meynert usually affected first
  - c) visuosensory and sensorimotor areas relatively spared until later
  - d) loss of synapses correlates best with degree of cognitive impairment
3. *Amyloid plaques* :
  - a) are the critical pathological feature of Alzheimer's disease - the plaques consist of amyloid peptide  $\beta$ -A4
  - b) extent correlates with severity of clinical illness
4. *Neurofibrillary tangles* :
  - a) abnormal phosphorylation of 'tau' proteins implicated in AD – e.g. A68 protein (Alzheimer disease associated protein – ADAP)
  - b) the degree of cognitive impairment correlates with the number of neurofibrillary tangles
5. *Glial proliferation*
6. *Granulovascular degeneration* :
  - a) especially in hippocampus

### Neurochemistry

1. *Cholinergic loss* :
  - a) substantial depletion of choline acetyltransferase (CHAT) and acetylcholine esterase is found, mainly in the temporal cortex
  - b) reduced cholinergic cells in nucleus basalis of Meynert, medial septum, diagonal band
  - c) cholinomimetics may improve cognitive deficits
2. *Noradrenergic loss* :
  - a) reduced noradrenaline concentrations in the cortex and hippocampus
  - b) cell loss in locus coeruleus, especially in early onset AD
  - c) correlates with depression in AD
3. *Serotonergic loss* :
  - a) loss of cortical 5-HT<sub>2</sub> receptors – especially in frontal and temporal lobes
  - b) cell loss and neurofibrillary tangles in nucleus raphe dorsalis
4.  $\beta$ -A4 amyloid may be neurotoxic, possibly altering calcium homeostasis and thereby altering neuronal susceptibility to the effects of excitotoxins such as glutamate
5. decreased somatostatin
6. decreased GABA
7. decreased CK

8. deficiency of mitochondrial alpha ketoglutarate dehydrogenase complex or pyruvate dehydrogenase complex

### Immunology

- localized inflammatory reaction
- complement found in senile plaques
- neuroglial reaction to amyloid
- increased acute phase reactants

### Clinical features

- memory loss (STM > LTM)
- personality changes
- depression
- anxiety
- inability to perform at normal level in everyday decision making
- perceptible delay in word finding
- speech can be hesitant
- early dementia is probable with a MMSE score of 24-27
- problems of language, praxis, and gnosis become increasingly apparent as the disease progresses
- personal care deteriorates
- extrapyramidal features often emerge with the appearance of primitive reflexes and sometimes myoclonus

### Investigations

#### Psychometry :

- delayed recall is the best overall discriminator for early Alzheimer's disease

#### Electrophysiology :

- slowing of the dominant  $\alpha$  rhythm
- appearance of  $\theta$  and  $\delta$  activity
- the P300 component of event-related potentials is either depressed or delayed

#### SPECT :

- symmetrical reduction in grey matter perfusion, the degree of which correlates with the severity of dementia
- the earliest changes are seen in the temporoparietal cortex

#### PET :

- bilateral reduction of oxygen use and glucose uptake, initially in the temporal lobes but later involving the frontal lobes

#### CT :

- temporal lobe volume is reduced
- serial scanning can show progressive volume loss

### Management

- cholinesterase drugs such as DONEZEPIL (ARICEPT<sup>®</sup>) have a role in delaying onset of the disease

- depressive symptoms are best treated with SSRIs which are better tolerated
- low doses of neuroleptics are advised

### **Dementia of frontal lobe type (FLD)**

- 2<sup>nd</sup> most common form of dementia in the pre-senium
- cortical degeneration occurs mainly in the frontal lobes and is non-specific, with neural loss, slight gliosis, and spongiosis
- more common in men
- 50 % of patients have a family history
- onset usually in the mid-fifties
- normal duration is 7-10 years
- EEG is normal
- ? variety of Pick's disease

#### **Clinical features**

- personality change
- social disinhibition
- progressive dementia
- relative sparing of memory loss and spatial impairment

### **Pick's disease**

#### **Epidemiology**

- makes up 5 % of dementias
- most cases start between 50 - 60
- F:M = 2:1

#### **Aetiology**

- possibly a single autosomal dominant gene, with variable penetrance

#### **Pathological features**

- pathology is circumscribed asymmetrical atrophy of the frontal and/ or temporal lobes accompanied by a lesser degree of general atrophy
- severe neuronal loss in the outer layers of the atrophic cortex with argentophilic inclusions (Pick bodies) and swollen chromatophilic neurones (Pick cells)
- 'knife blade' atrophy is seen due to neuronal loss
- increased concentrations of zinc in the brain and red blood cells, with increased excretion of zinc in the urine
- senile plaques or neurofibrillary tangles are absent

#### **Clinical features**

- frontal lobe changes :
  - changes of character and social behaviour

- diminution of drive
- lack of restraint may lead to stealing, alcoholism, and sexual misadventures
- impairment of intellect and memory
- predominant mood is fatuous euphoria
- speech becomes perseverative
- condition is progressive, with death after 2-10 years

### Investigations

- EEG shows a lower incidence of abnormalities than Alzheimer's
- CT shows :
  - marked atrophy affecting the anterior portions of the frontal and temporal lobes
  - enlargement of the frontal horns

### Huntington's chorea

- described in 1872 by George Huntington

### Epidemiology

- estimated prevalence = 4-7 per 100000
- equal sex ratio
- age at onset is usually 25-50

### Aetiology

- autosomal dominant gene with 100 % penetrance
- due to a trinucleotide repeat mutation - proximal arm of chromosome 4; all cases can be accounted for by this mutation
- decreased levels of GABA in the caudate nucleus
- decreased GABA biosynthesis and increased dopamine concentrations in parts of the basal ganglia

### Pathology

- pathological changes occur mostly in the frontal lobes and caudate nucleus; the basal ganglia are atrophied

### Clinical features

- usually begins in the 3<sup>rd</sup> or 4<sup>th</sup> decade (mean age is in the forties)
  - 10 % present before the age of 20
  - 10 % occur after 60
- onset of neurological and psychiatric symptoms may be many years apart
- **neurological signs :**
  - choreiform movements of the face, hands, and shoulders which are sudden, unexpected, aimless, and forceful
  - associated with changes in gait and dysarthria
  - eventually results in gross writhing contortions and ataxia
  - extrapyramidal rigidity and epilepsy also occur

- **psychiatric symptoms :**
  - dementia occurs in the later stages, after the development of chorea
  - cortical destruction is more extensive than in Alzheimer's and vascular dementias
  - memory is less affected
  - insight is often retained at a late stage
  - distractibility is characteristic, with reduced ability to regulate attention and psychomotor speed
  - depressive symptoms are frequent
  - *higher risk of suicide*, including those in the family not affected
  - paranoid symptoms are common, and schizophrenia may occur more frequently than in the general population

### Investigations

- CT shows caudate atrophy
- PET scanning shows a reduces striatal metabolism
- SPECT shows altered caudate and putaminal blood flow
- EEG is 'flat'

### Management

- phenothiazines and butyrophenones for choreiform movements
- pallidectomy and thalamotomy have been used but there is a risk of worsening the dementia or causing neurological side effects
- antidepressants are used for major depressive symptoms

### Prognosis

- adults : 13-16 years to death
- children : 8 years to death

## **Prion diseases (Creutzfeldt-Jacob Disease)**

- transmitted by blood or tissues between human beings
- rapidly progressive degenerative disease of the nervous system

### Epidemiology

- 50-100 cases occur each year in the UK
- equal sex ratio
- onset is 40-60

### Aetiology

- due to accumulation of an abnormal prion protein in the brain (prions are small proteinaceous particles that resist inactivation by procedures that modify nucleic acid)
  - encoded on **chromosome 20**
- individuals with the E4 allele of apolipoprotein ε are at a higher risk of developing the disease

- the familial form (*Gerstmann-Straussler-Scheinker*) accounts for 10 % of patients and principally affects the cerebellum
  - autosomal dominant

### Clinical features

- personality change
- seizures
- intellectual deterioration
- neurological deficits including :
  - cerebellar ataxia
  - spasticity
  - extrapyramidal signs
  - myoclonus sensitivity to noise or touch
- in new-variant CJD (nvCJD), initial psychiatric symptoms are followed by a cerebellar syndrome leading to memory failure and akinetic mutism
- 4 forms :
  - subacute spongiform encephalopathy (SSE 1), rapidly fatal
  - SSE 2 (*Heidenhaim's* – blindness and dementia)
  - thalamic form
  - ataxic form

### Investigations

- **EEG :**
  - abnormal in 90 %
  - low voltage with bi/ triphasic discharges
  - repetitive complexes that coincide with the myoclonus
- atrophy may be apparent in the later stages with CT or MRI
- the CSF protein is sometimes moderately elevated

### Prognosis

- rapidly progressive over 1-2 years

### Normal pressure hydrocephalus

- not due to a block within the ventricular system but there is an obstruction in the subarachnoid space so that CSF can escape from the ventricles but is prevented from flowing over the ventricles
- more common in the elderly

### Aetiology

- may be a history of SAH, head injury or meningitis

### Clinical features

- progressive memory impairment and *dementia*
- slowness
- marked unsteadiness of *gait*

- urinary *incontinence*

#### Investigations

- removal of 50 ml of CSF can lead to a temporary improvement in cognition
- CT or MRI shows dilatation of the ventricular system and relatively normal sulci; periventricular lucencies are found on MRI

#### Management

- shunt to improve the circulation of CSF
- often the dementia may not improve

## **Classification of dementia and Alzheimer's disease.**

### **Morris JC**

After AD, the most common causes of dementia are vascular dementia and dementia in persons with Parkinson's disease. Less common dementias include progressive supranuclear palsy, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, and inherited metabolic disorders, most of which are extremely rare. Identifying the cause of dementia is important because some forms can be treated with currently available therapies. In instances involving genetically transmitted disease, genetic testing and counseling of family members may be advisable.

## **Is early-onset Alzheimer disease a distinct subgroup within the Alzheimer disease population?**

### **Raskind MA, Carta A, Bravi D**

Although patients with Alzheimer disease (AD) share major clinical and neurohistologic features regardless of age of onset, the hypothesis that early-onset AD comprises a distinct subgroup remains viable. Most studies addressing this hypothesis find quantitative differences between early- and late-onset AD patients. Early-onset AD is characterized by shorter survival, more rapid cognitive deterioration, greater frequency of language disturbance, more severe and widespread neurochemical abnormalities, and a greater density of neurohistologic lesions. In addition, both the chromosome 14 genetic abnormality and chromosome 21 amyloid precursor protein mutations appear restricted to early-onset familial AD. Age of onset of AD subjects may be relevant to the design of clinical trials. For example, the efficacy of a drug that slows disease progression may be more easily demonstrated in subjects with early-onset disease.

## **Senile dementia and presenile dementia.**

**Nakamura S**

Department of Neurology, Faculty of Medicine, Kyoto University.  
Neurotransmitters including acetylcholine, dopamine, norepinephrine, serotonin, GABA and vasopressin were examined in control subjects and patients with Alzheimer-type dementia, involving presenile and senile dementia. Neurotransmitters exhibited various mode of changes with aging. Abnormalities found in senile or presenile dementia were not always parallel to the age-related changes. These results suggest that Alzheimer-type dementia cannot be understood as an accelerated senescence, but other etiological factors might be introduced for the manifestation of the dementia. Moreover, the disturbance in neurotransmitters revealed a difference between presenile Alzheimer's disease and senile dementia, indicating that further studies should be carried out taking the age of onset into consideration.

## **Presenile dementia with motor neuron disease.**

**Mitsuyama Y**

Department of Psychiatry, Miyazaki Medical College, Japan.  
Seventy-one Japanese cases of presenile dementia with motor neuron disease were reviewed. The clinico-pathological features were: (1) progressive dementia with insidious onset, mostly in the presenile period; (2) neurogenic muscular wasting in the course of illness (ALS- or SPMA-like symptoms); (3) duration from the onset of the illness to death: 2-5 years (average 30.6 months); (4) extrapyramidal symptoms and definite sensory deficits are less commonly present; (5) no characteristic abnormalities in the CSF or EEG; (6) no known consanguinity or familial occurrence; (7) non-specific mild to moderate degenerative changes in the fronto-temporal cerebral cortex, hypoglossal nuclei and spinal cord, and frequently in the substantia nigra. The author was interested in discovering whether the frequency and topology of lesions in the brain of patients with presenile dementia and motor neuron disease differed characteristically from the distribution found in cases of Alzheimer's disease, Pick's disease, Creutzfeldt-Jakob disease or progressive subcortical gliosis. Presenile dementia with motor neuron disease might be a new disease entity.

## **Chromosome changes in Alzheimer's presenile dementia.**

**Buckton KE, Whalley LJ, Lee M, Christie JE**

Lymphocyte chromosomes were examined in 36 patients with Alzheimer's presenile dementia, 36 healthy, age and sex matched controls, and 36 sex matched, non-demented, elderly controls, approximately 20 years older than the Alzheimer patients. Increased chromosome aneuploidy was found in females with Alzheimer's disease but not in male subjects. Chromosome abnormalities observed in female patients were

similar to those observed in elderly controls, though in this latter group there was an increase in the frequency of cells that had lost an X chromosome. In the female Alzheimer patients and the elderly controls, there was an increase in the frequency of autosomal aneuploid cells but no single chromosome was preferentially affected. Because the chromosome abnormalities found in Alzheimer's disease are similar in nature but not as extensive as those observed in senescence in the absence of dementia, it is argued that chromosome aneuploidy is more likely to be related to processes concerned with ageing rather than being specifically linked to the dementia of Alzheimer's disease.

## **Primary presenile dementia: the use of the visual evoked potential as a diagnostic indicator.**

**Harding GF, Wright CE, Orwin A**

The use of the flash and pattern reversal visual evoked potential (VEP) in the diagnosis of primary presenile dementia was investigated. The results from 20 patients with primary presenile dementia were compared with those from a control group of normals of equivalent age and from a control group of 20 patients with cortical atrophy but no dementia. Presenile dementia caused a slowing of the major positive (P2) component of the VEP to flash stimulation. However, the VEP to pattern reversal stimulation (P100) was of normal latency. The difference between these two latencies characterises this unusual combination of results and is found to be a more specific diagnostic indicator of primary presenile dementia than the EEG or CT scan.

## **Neuropsychiatric studies in a family with presenile dementia different from Alzheimer and Pick disease.**

**Gydesen S, Hagen S, Klinken L, Abelskov J, Sorensen SA**

Institute of Medical Genetics, University of Copenhagen, Denmark.

We have studied a family in which 14 persons among 73 are or have been suffering from presenile dementia. Post mortem examination showed atrophy but no sign of any known demential syndrome. Cerebral blood flow measured in the late stage of disease was low, but with no characteristic pattern in flow distribution. In one patient in the initial stage of disease, the cerebral blood flow was unexpectedly increased. The patients with presenile dementia in this family did not reveal pathological signs of any known demential syndrome and showed CBF-changes not earlier reported. Moreover, contrary to widely held views we have evidence that dementia may be connected to a high blood flow at least in the initial state. An increased blood flow was also seen in seven of ten well functioning first degree relatives, in some cases along with cerebral atrophy and/or psychological tests with signs of dementia. Are these people going to develop manifest dementia later in life?

## **EEG and cognitive impairment in presenile dementia.**

EEG and psychometric findings were studied in a group of 57 patients consisting of 19 cases of Alzheimer's disease, 7 cases of Pick's disease, 24 cases of cerebrovascular **dementia** (CVD) and a group of 7 cases with **dementia** of various other aetiology. The diagnoses have so far been confirmed by autopsy in 23 out of 57 cases. EEG was evaluated by means of visual inspection. Psychometric studies enabled a **classification** into 5 psychometric defect groups according to the degree of **dementia**. An overall good correlation was found between the degree of **dementia** and EEG abnormality. A significant correlation between the test score and the EEG was found only for the vocabulary test and paired associates test. However, on the reaction time test, colour word test, and Koh's block design test, large patient groups were untestable, and a highly significant correlation was found between non-testability and severely abnormal EEG. The Alzheimer and the CVD groups differed distinctly, most of the Alzheimer cases showing a severe or moderate degree of EEG abnormality and **dementia**, whereas in the CVD cases, the **dementia** was less pronounced and the EEG often normal or only slightly abnormal. Four out of seven cases of Pick's disease had a normal EEG, which distinguished them from the Alzheimer cases which had a comparable psychometric defect.