

# Neuropathology

## *Dementia*

### **Alzheimer's disease**

#### Macroscopic neuropathology

- global brain atrophy (most marked in the frontal and temporal lobes)
- ventricular enlargement
- sulcal widening

#### Histopathology

- neuronal loss
- shrinking of dendritic branching
- reactive astrocytosis
- neurofibrillary tangles
- neuritic (senile) plaques
- histological changes commonly seen in the hippocampus include:
  - granulovacuolar degeneration
  - Hirano bodies
  - neurofibrillary tangles
  - neuritic (senile) plaques

#### Ultrastructural pathology

- neuritic plaques contain a core of amyloid
- scattered deposits of beta-amyloid have been found to localize to active microglia

#### Neurochemical pathology

- decreased:
  - Acetylcholinesterase
  - Choline acetyltransferase
  - GABA
  - noradrenaline

### **Pick's disease**

#### Macroscopic

- selective asymmetrical atrophy of the anterior temporal lobes and frontal lobes
- knife-blade gyri
- ventricular enlargement

#### Histopathology

- Pick's bodies
- neuronal loss

- reactive astrocytosis
- these changes are seen in:
  - cerebral cortex
  - basal ganglia
  - locus coeruleus
  - substantia nigra

#### Ultrastructural

- Pick's bodies consist of:
  - straight neurofilaments
  - paired helical filaments

### **Multi-Infarct dementia**

#### Macroscopic

- multiple cerebral infarcts
- local or general brain atrophy
- ventricular enlargement
- arteriosclerotic changes in major arteries
- total volume of the infarcts:
  - 50 – 100 ml: cognitive impairment
  - > 100 ml: dementia

### **Lewy body disease**

#### Histopathology

- Lewy bodies
- neuronal loss
- neurofibrillary tangles
- neuritic (senile) plaques
- compared to Parkinson's disease, the density of Lewy bodies is much higher in:
  - cingulate gyrus
  - parahippocampal gyrus
  - temporal cortex

#### Ultrastructural

- Lewy bodies contain:
  - protein neurofilaments
  - granular material
  - dense core vesicles
  - microtubule assembly protein
  - ubiquitin
  - tau protein

## **Creutzfeldt-Jakob disease**

### Macroscopic

- selective cerebellar atrophy
- generalized cerebral atrophy
- ventricular enlargement

### Histopathology

- status spongiosus
- neuronal degeneration without inflammation
- astrocytic proliferation

## **Punch-drunk syndrome**

### Macroscopic

- cerebral atrophy
- ventricular enlargement
- thinning of the corpus callosum
- perforation of the septum pellucidum

### Histopathology

- neuronal loss
- neurofibrillary tangles

# **Schizophrenia**

## **Gross neuropathology**

### Brain mass

- slight but significant reduction (Bruton *et al.* 1990)

### Brain length

- both hemispheres of formalin-fixed brains are shorter when compared to controls (Bruton *et al.* 1990)

### Cerebral volume

- in PM studies, there is a reduction in the volumes of the:
  - cerebral hemispheres
  - cerebral cortex
  - central grey matter
- the volumes of the white matter do not differ significantly

### Hippocampus and Parahippocampal gyrus

- the parahippocampal gyrus was significantly smaller in schizophrenic subjects
- some studies have found that in schizophrenics, the hippocampal formation was significantly smaller in the left and right hemispheres
  - the reduction in volume is greater in male subjects

### Ventricular volume

- a number of PM studies have found ventricular enlargement, especially of the temporal horn

### Temporal lobe

- the majority of PM studies have found a reduction in temporal lobe volume, especially affecting the grey matter of the amygdala and anterior hippocampus

## **Morphometric studies**

### Temporal lobe

- pyramidal cell disorientation in the hippocampus
- lower pyramidal cell density in the left CA4 hippocampal region
- cytoarchitectural abnormalities in the entorhinal cortex:
  - aberrant invaginations of the surface
  - disruption of cortical layers
  - heterotropic displacement of neurons
  - paucity of neurons in superficial layers
- smaller neurone size in the hippocampus
- distorted distribution of NADPH-d neurones in the hippocampal formation and in the neocortex of the lateral temporal lobe

### Other cortical areas

- lower neuronal density in the following regions:
  - prefrontal cortex: layer VI
  - anterior cingulate cortex: layer V
  - primary motor cortex: layer III
- glial density tends to be lower in these areas

### Synaptic pathology

#### Synaptic vesicles

- large numbers of synaptic vesicles in presynaptic knobs found in schizophrenic brains

#### Synaptophysin

- in schizophrenic brains, synaptophysin mRNA is reduced in:
  - CA4
  - CA3
  - the subiculum
  - the parahippocampal gyrus

### Gliosis

- most recent studies have not shown significant gliosis

## ***Movement disorders***

### **Parkinson's disease**

#### Macroscopic

- depigmentation of the substantia nigra, especially in the zona compacta
- depigmentation of the locus coeruleus
- diffuse cortical atrophy can take place

#### Histopathology

- neuronal loss
- reactive astrocytosis
- Lewy bodies in:
  - substantia nigra
  - dorsal motor nucleus of the vagus
  - hypothalamus
  - nucleus basalis of Meynert
  - locus coeruleus
  - Edinger-Westphal nucleus
  - raphe nuclei
  - cerebral cortex
  - olfactory bulb
- presence of melanin-containing macrophages

#### Neurochemical

- reduced inhibitory dopaminergic action of the nigrostriatal pathway on striatal cholinergic neurones

### **Huntington's disease**

#### Macroscopic

- small brain with reduced mass
- marked atrophy of the corpus striatum, particularly the caudate nucleus
- marked atrophy of the cerebral cortex, particularly the frontal lobe gyri
- dilatation of the lateral and third ventricles

#### Histopathology

- neuronal loss in the cerebral cortex, especially the frontal cortex
- neuronal loss in the corpus striatum, particularly neurones using as neurotransmitters:
  - GABA and enkephalin
  - GABA and substance P
- astrocytosis in affected regions
- sparing of:
  - diaphorase-positive neurones containing nitric oxide synthase

- large cholinesterase-positive neurones

#### Neurochemical

- ↓ GABA
- ↓ Glutamic acid decarboxylase
- ↓ Acetylcholine
- ↓ Substance P
- ↓ CRF
- ↑ somatostatin
- dopamine hypersensitivity

## ***Tardive dyskinesia***

- various theories:
  1. dopamine hypersensitivity
  2. free radical induced neurotoxicity
  3. GABA insufficiency
  4. noradrenergic dysfunction

### **Dopamine hypersensitivity hypothesis**

#### Proposed mechanism

Long- term treatment → chronic dopamine receptor blockade → D2 receptor hypersensitivity in the nigrostriatal pathway → tardive dyskinesia

#### Evidence in favour

- studies of denervation-induced hypersensitivity in muscles
- animal experiments in which, following the discontinuation of antipsychotic drugs, acute dopamine agonist challenges → increased oral stereotyped behaviour
- animal experiments in which repeated antipsychotic treatment may lead to increased D2 receptor levels

#### Problems with the theory

- differences in the chronology of onset of symptoms in animal and human models
- PM studies in humans have not shown significant differences in schizophrenic brains with or without TD
- blood biochemical assays have not shown significant differences between patients with TD and patients without TD with respect to:
  - prolactin
  - somatotrophin
- dopamine agonists do not strikingly exacerbate tardive dyskinesia
- dopamine antagonist antipsychotics may sometimes worsen TD

### **Free radical induced neurotoxicity**

#### Proposed mechanism

Long- term treatment → increased catecholamine turnover → free radical byproducts → membrane lipid peroxidation in the basal ganglia → tardive dyskinesia

#### Evidence in favour

- vitamin E is of benefit in rodent models of TD
- some studies have shown increased blood or CSF levels of lipid peroxidation byproducts in patients with TD compared to those without TD

#### Problems

- Vitamin E treatment of TD does not work

## **GABA insufficiency**

### Proposed mechanism

Long-term treatment → destruction of GABAergic neurones in the striatum → reduced feedback inhibition → TD

or

Long-term treatment → reduced GABAergic activity in the pars reticulata of the substantia nigra → reduced inhibition of involuntary movements → TD

### Evidence in favour

- antipsychotic-treated dyskinetic monkeys have a decrease in glutamic acid decarboxylase in the basal ganglia
- patients with TD have been found, on PM, to have a reduced level of in glutamic acid decarboxylase in the subthalamic nucleus
- GABAergic agonists such as BZDs, baclofen, and gamma-vinyl GABA have shown promise as therapeutic agents

### Problems

- rodent models do not show consistent changes in GABA function with neuroleptic treatment
- GABA agonists are not yet effective treatments

## **Noradrenergic dysfunction**

### Mechanism

- noradrenergic overactivity contributes to the pathphysiology of TD

### Evidence in favour

- patients with TD have significantly higher dopamine  $\beta$ -hydroxylase activity
- platelet alpha-2 adrenoceptor binding and CSF noradrenaline have been correlated with the severity of TD

### Problems

- TD cannot be treated with noradrenergic drugs