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
  - heterotrophic 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**

• \( \downarrow \) GABA
• \( \downarrow \) Glutamic acid decarboxylase
• \( \downarrow \) Acetylcholine
• \( \downarrow \) Substance P
• \( \downarrow \) CRF
• \( \uparrow \) 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 β-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