

Nervous system 5 "The rest"

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Topics to be covered

- demyelinating disease
- degenerative disease
- (metabolic and toxic disease)
- developmental disease/malformations
- hydrocephalus

Demyelinating disease

- only common one is multiple sclerosis

Multiple sclerosis (MS)

- primary change is loss of myelin, hence problems with electrical transmission
 - relative sparing of neurons to begin with
- 1: 1000 incidence in whites
 - highest incidence of all in Scotland
- ?100x lower incidence in black Africans, but increasing
- genetic factors important
 - much commoner if family member affected

Multiple sclerosis

- usually starts in youth or early adulthood
- distinctive relapsing, remitting course even over many years
 - relapses followed by at least partial recovery
 - fewer relapses with time, but usually progressive neuron damage occurs
- focal "plaques" of demyelinated white matter
 - size range from microscopic to several cms. across
 - myelin loss, reduced numbers of oligodendrocytes, often some oedema
 - surrounding infiltration of lymphoid cells and macrophages

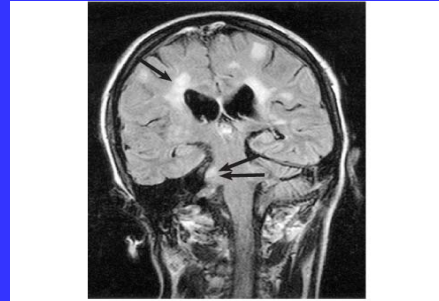
Multiple sclerosis

- autoimmune disease
 - T helper cell mediated, especially CD 4+ cells
 - damage often occurs first round venules
- as plaques heal, fewer inflammatory cells (? vice versa) and gliosis may occur
- undamaged axons around plaques may show abnormal myelination
 - ? an attempt at repair/replacement

MS - clinical effects

- depend on site of plaques
 - first presentation often optic neuritis
 - but not all optic neuritis progresses to MS
 - also cranial nerve defects, ataxia, nystagmus etc
 - even cord lesions (motor or sensory)
- CSF
 - protein levels usually slightly raised
 - particularly immunoglobulin levels
 - may also be increase in cells

MS plaques - NMR



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Multiple sclerosis plaque (stained for myelin)



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Other demyelinating diseases

- other rarer demyelinating diseases
 - after systemic infection (especially virus or mycoplasma)
 - or following immunisation

Degenerative diseases of the brain

- an unrelated group of many diseases
- common feature is progressive neuron loss as primary change
- site selective affect according to disease
- usually no clear aetiology
 - though genetic factors important in some
- often proteinaceous aggregates from damaged/dead neurons remain in brain as cellular inclusions
 - can be diagnostic
 - but can also increase local damage

Degenerative diseases of the brain

- cortex
 - Alzheimer's disease
 - vascular dementia
- basal ganglia and brainstem
 - Huntington's disease
 - Parkinson's disease
- motor neurons
 - amyotrophic lateral sclerosis

Cortex - Alzheimer's disease

- commonest cause of dementia in elderly in "the west"
- mostly sporadic, but can be familial
- insidious onset, but always progressive
 - disorientation, memory loss, aphasia etc
 - within ~ 5-10 yrs patients become mute & immobile
 - major medical, social, financial burden
- rare before age 50, but then exponential rise in incidence

Alzheimer's disease

- cerebral cortical atrophy, which is not uniform
 - widened sulci, narrow gyri
- ventricles dilate in compensation ("hydrocephalus ex vacuo")
- very typical microscopic findings
 - though all present to lesser degree in "normal" elderly (and other ageing primates)
- dementias in general are common, so typical clinical findings and pathology necessary for specific diagnosis of Alzheimer's

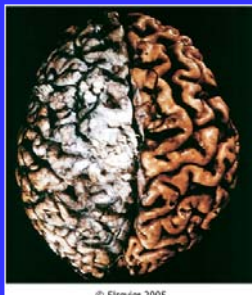
Alzheimer's disease - pathology

- senile plaques
 - microscopic balls made up of degenerate neuronal contents
 - often central core of amyloid
 - older plaques have halo of reactive glial cells
- neurofibrillary tangles
 - bundles of filaments from degenerate neurons sited beside or around nuclei of neurons
 - tau protein (from axons) a major component
- amyloid in small vessels

Alzheimer's disease

- amyloid important in pathogenesis
- one of transmembrane proteins in normal neurons is "amyloid precursor protein"
 - normally breaks down into soluble peptides
 - but here produces insoluble A β peptide in "pleated sheets"
 - ? genetic make up helps determine this
 - A β form very resistant to proteolysis and so removal (also probably elicits reactive glial response)
 - A β accumulation probably critical to disease development - ? directly neurotoxic
 - not clear if reactive glial cells hinder or help disease development

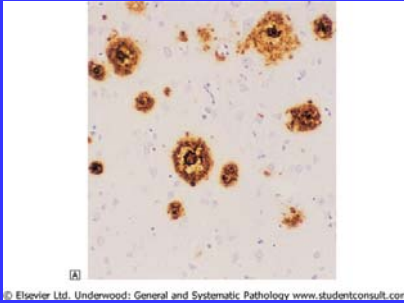
Alzheimer's disease



Alzheimer's disease



Alzheimer's – senile plaques



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Alzheimer's disease – neurofibrillary tangle



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Cortex - dementias other than Alzheimer's

- several different varieties
- only common one is vascular dementia
 - probably due to microscopic foci of cortical ischaemia, caused by all usual forms of degenerative vascular disease
 - atheroma, hypertension, microthrombi or microemboli etc

Degenerative diseases – basal ganglia and brain stem

- again lots of diseases, but only important ones are –
 - Huntington's disease
 - because of its clear hereditary nature
 - Parkinson's disease
 - because it's common

Basal ganglia - Huntington's disease

- progressive movement disorder, often accompanied by dementia
- autosomal dominant condition, but adult onset
- affects neurons in caudate nucleus and putamen, which atrophy
 - ventricles may dilate as a result
- typically choreiform movements, since basal ganglia help modulate motor output
- ? again an abnormal protein disorder, with accumulation causing neuronal damage

Brainstem - Parkinson's disease

- loss of neurons and gliosis in substantia nigra and locus ceruleus of brainstem
- again once commoner in "the west"
 - especially in older individuals
- but affects all regions and races
 - also increasing incidence with age
- disease genetics being established
 - ? will this be another case where altered cell protein induces disease

Parkinson's disease

- affected neurons normally pigmented, so sites become pale as neurons lost
- characteristic "Lewy body" inclusions in affected neurons
 - again mostly filaments from intracellular proteins
- affected neurons loss also means dopamine (and noradrenaline) loss
 - severity of effects ~ dopamine loss
 - ("replacement" with L-DOPA used therapeutically)

Normal substantia nigra



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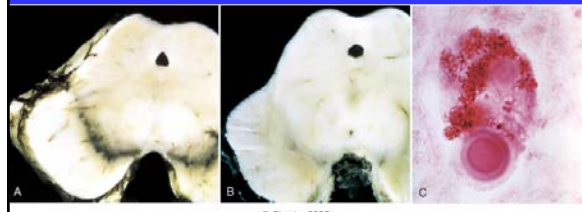
Parkinson's disease



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edition

Parkinson's disease



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Parkinson's disease

- progressive disease even if treated
- first signs often 1) movement disorders
 - face
 - posture
 - gait
- or 2) tremor
- also often cognitive impairment, leading to dementia

Degenerative diseases of motor neurons

- only important one is amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (motor neurone disease)

- muscle atrophy and hyper-reflexia
 - due to spinal anterior horn neuron loss
 - +/- cranial nerve neuron loss
 - affected neurons show autophagic vacuoles
- most common in 50s and can be familial
 - genetic loci known for familial cases
 - wide variety of mutations, but precise cause of disease unknown
- classically starts with weakness of hands
 - then extends proximally
 - eventually involving respiratory muscles

Metabolic and toxic diseases

- genetic
 - several of them, but rare
- toxic and acquired
 - vitamin deficiency (B1 and B12)
 - hypo- and hyperglycaemia
 - hepatic encephalopathy
 - ethanol, methanol, CO, irradiation

Developmental disease and malformations

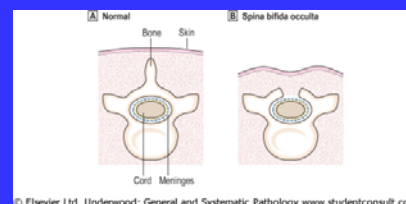
- 1 - 2 % all births
- include cerebral palsy and retardation, which can be due to a variety of causes
- two to remember
 - neural tube defects
 - syringomyelia/hydromyelia

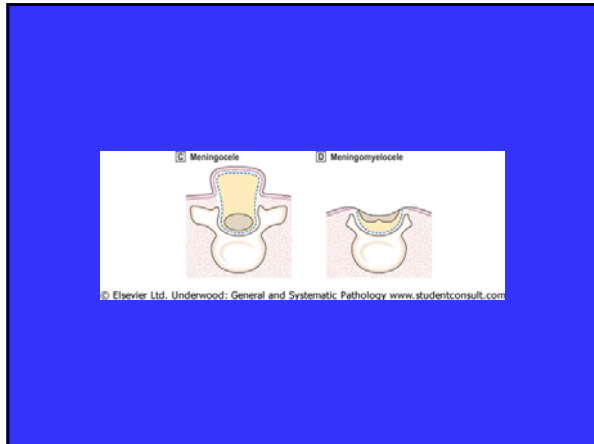
Neural tube defects

- only common congenital NS malformations
- due to focal failure of neural tube to close or to its reopening
- can involve bone/soft tissues +/- meninges +/- nervous tissue
 - clinical problems arise when neural tissue involved or if there is secondary infection
- aetiology - ?? folate deficiency a factor
- can be diagnosed prenatally via maternal blood of fetoprotein (AFP) levels and imaging

Neural tube defects

- usually spinal involvement
 - *spina bifida occulta* (bone only) – usually no effect
 - *meningocoele* (meninges protrude through defect)
 - *meningomyelocoele* (meninges and neural tissue protrude through defect)
 - most commonly lumbosacral areas
 - motor and sensory problems in legs, bowel, bladder
- very rarely can involve brain
 - cause anencephaly (no brain or calvarium)
 - incompatible with life





Syringomyelia/hydromyelia

- congenital disease of cord
- appearance of long “cysts” (“syringo”) in cord or dilatations of cord canal (“hydro”) itself
 - single or multiple
 - can extend and expand with time
 - rarely extend into brainstem (syringobulbia)
- pressure effects destroy NS tissue
 - classically present with pain & sensory loss in arms
- no clear cause
 - sometimes associated with maldevelopment of posterior fossa (Arnold Chiari malformation)

• and finally -

Hydrocephalus

- excess CSF in ventricular system
 - usually impaired flow and/or reabsorption
 - rarely excess secretion (choroid plexus tumours)
 - (cf. “hydrocephalus ex vacuo”, where ventricles dilate to make up for parenchymal loss)
- expands ventricles (400-500 mls CSF produced a day) and raises ICP
 - so neuronal loss, herniation etc
- (if before bony suture fusion, head enlarges)

Normal CSF pathway

- lateral ventricles
- foramen of Munro
- third ventricle
- cerebral aqueduct
- fourth ventricle
- foramina of Luschka/Magendie
- arachnoid granulations

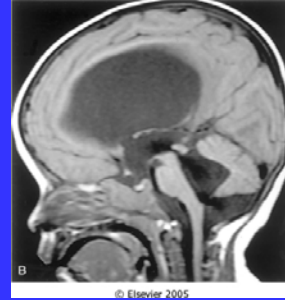
Hydrocephalus

- communicating (whole ventricular system)
 - e.g. “normal pressure hydrocephalus”, subarachnoid haemorrhage, meningitis, carcinomatous meningitis
- non-communicating (obstructed ventr. system)
 - acquired, e.g. tumours, subarachnoid haemorrhage
 - congenital - various malformations
- pressure can be relieved by releasing CSF
 - ventriculoperitoneal shunt
 - (risk of NS infection)

Ventricular dilatation in hydrocephalus



Hydrocephalus on NMR



CT scan: chronic hydrocephalus

