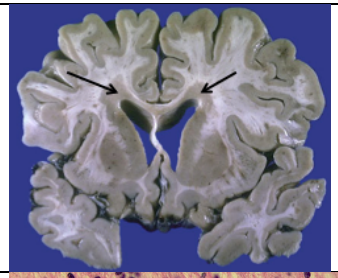
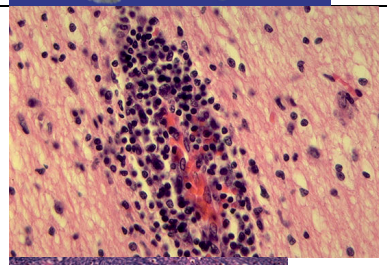
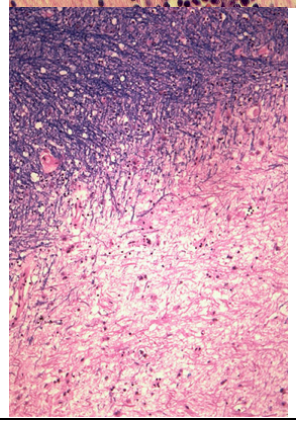
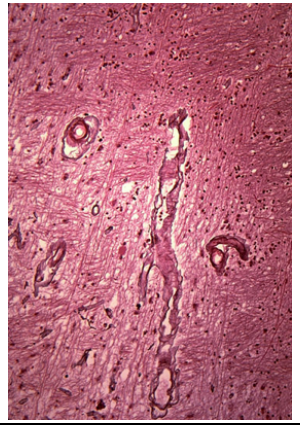
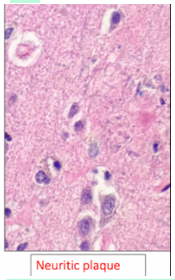
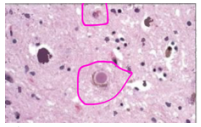
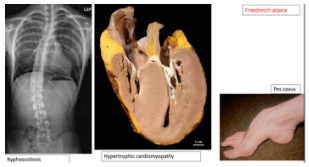
CNS PATH: Demyelinating Disorders

Leukodystrophies: Demyelinating Disorders – Multiple Sclerosis

MULTIPLE SCLEROSIS	
DEFINITION	Autoimmune demyelination & sclerosis of white matter 'separated in time & space' – ***lesions are in different areas & are different ages***; Though to have a post-infectious mechanism
PRESENTATION	20-40 y/o female with history of **transient sensory & motor symptoms** *Unilateral vision impairment, ataxia,* ***intranuclear opthalmoplegia (INO)****, spasticity****, poor bladder control*** ***Often times the brain imaging will look worse than the patient is presenting**
GROSS	 **PERIVENTRICULAR PLAQUES**: *greyish sunken areas of WHITE MATTER & represent the* ***gliotic scar*** *of an old demyelinated lesion*
HISTOLOGY	 **Perivascular Cuffs**: lymphocytes + macrophages present in demyelinated plaques; ***immunological attack on cerebral white matter***  **Luxol Fast Blue** for myelin → DEMYELINATION in plaque **Pale thin strands within are the remaining axons*  **Bodian** stain for axons → ***'loss of myelin but preservation of axons in MS plaques*** **Still participate in salutatory conduction of impulses but the rate of travel is slower (unmyelinated)*

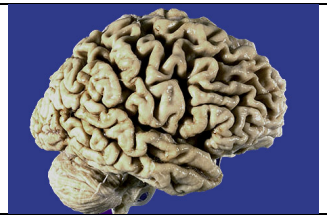
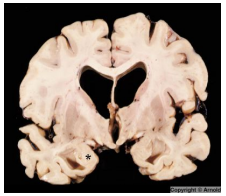
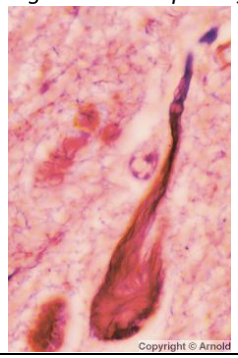
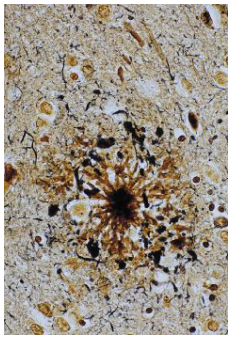
Demyelinating disorders				
Leukodystrophy • Inherited mutations in the enzymes of myelin production • Young age • White matter becomes grey • ↓ motor skills→ ataxia, hypotonia, spacisity **3 types** ↳↓muscle tone Metachromatic leukodystrophy • Sulfatides accumulate in oligodendrocytes • Feeding difficulties, blindness, deafness Krabbe disease • Galactocerebroside accumulate in glial cells & macrophages • Feeding difficulties, blindness, deafness • fatal Globoid Cells Adrenoleukodystrophy • Fatty acids accumulate in adrenals & glial cells • Feeding difficulties, blindness, deafness • Addisons disease	**Multiple Sclerosis** • Autoimmune destruction of CNS myelin & oligodendrocytes • Women, young adults • Associated w/ HLA-DR2 • Blurry vision, vertigo, scanning speech, unilateral loss of sensation • Neuro defects = off & on **Diagnosis** • Plaques on MRI • ↑ Oligoclonal IgG bands	**Subacute Sclerosing Panencephalitis** Aka Dawsons disease • Due to persistent measles virus infection of brain • Infection in infancy, signs = later on in life • Poor school performance, forgetfulness, sleeplessness→ death	**Progressive Multifocal Leukoencephalopathy** • JC virus infection, immunosuppression (AIDS, leukemia) • Rapidly progressing neuro signs→ death	**Central Pontine Myelinolysis** • • 2-6 days after rapid correction of hyponatremia • Rapidly evolving quadriplegia, locked in syndrome
Degenerative disorders: loss of neurons in grey matter due to protein accumulation→ damaged neurons				
Alzheimer's • Cortex degeneration • MCC of dementia **Sporadic (old age)** • 95% = mutations in E4 of APOE **Familial (younger age)** • Presenilin 1 & 2 mutations • Alzheimer's develops in Down syndrome (trisomy 21) pts by ~40yrs	**Parkinson's** Movement lost then memory • Brainstem, basal ganglia & cerebellum degeneration leads to movement disorders→ Parkinson's & dementia w/ lewy body • loss of dopaminergic neurons in the substantia nigra of the basal ganglia	**Huntington** Movement disorder- caudate nucleus, striatum, basal ganglia • degeneration of GABAergic neurons • CAG repeats in huntington gene • Choera, dementia @ ~40yrs • suicide = common	**Friedreich ataxia** Movement disorder- cerebellum & spinal cord • AR disorder affecting cerebellum & spinal cord • Unstable GAA repeats in frataxin gene **Clinical** • Ataxia, staggering gait, nystagmus, dysarthia, pes cavus,	**ALS** Motor neuron disease aka Lou Gehrig's disease • Sporadic Mutation in superoxide dismutase 1 • Misfolded SOD 1 triggers neuronal death • **40-60yrs** • Atrophied & weak muscles (LMN) & spastic + hyperreflexia (UMN)

Clinical • Slow onset memory loss, changes in behavior & personality **Morphology** • Neurotic/amyloid plaques (AB)(extracellular)  • Neurofibrillary tangles (tau proteins) • **Cerebral atrophy**	**Microscopy** • a-synuclein aggregates (Lewy body)  **Clinical** • pill rolling tremor @ rest, disappears w/ movement • NO MOTOR WEAKNESS • Expressionless Face		kyphoscoliosis in children 	+ POSITIVE + Babinski

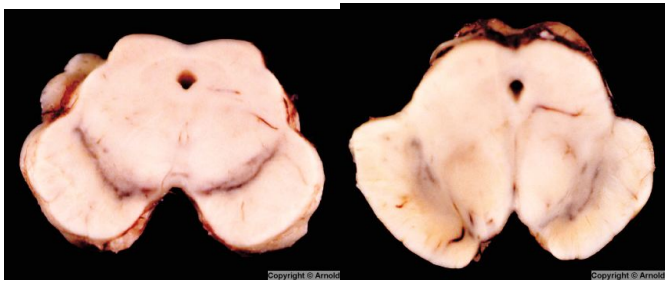
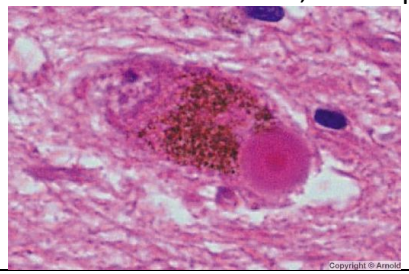
CNS PATH: Degenerative Diseases

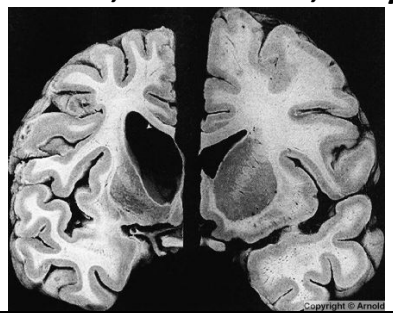
Location of Degeneration	
CORTEX	**Alzheimer's Disease** **Pick's Disease & other Frontotemporal Dementias (FTD)** **Diffuse Lewy Body Disease** **Corticobasal Degeneration (CBD)** **FTLD-U (Frontotemporal Lobar Degeneration)**
CAUDATE	**Huntington's Disease**
MIDBRAIN	**Parkinson's Disease (Idiopathic)** **Multiple System Atrophy (MSA): Striatonigral Degeneration, Olivopontocerebellar Degeneration, Shy Drager Syndrome** **Progressive Supranulcear Palsy**
SPINOCEREBELLAR DEGENERATION	**Spinocerebellar Ataxias (CAG repeat)** **Friedreich's Ataxia**
MOTOR SYSTEM	**Amyotrophic Lateral Sclerosis (ALS)** Spinomuscular Atrophy

Protein Aggregate	
β-AMYLOID	**Alzheimer's Disease**
TAU PROTEIN "Tauopathies"	**FTDP-17 (Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17):** familial dementia **Pick's Disease** **Corticobasal Degeneration (CBD)** **Progressive Supranuclear Palsy**
SYNUCLEIN "Syncucleinopathies"	**Parkinson's Disease (Idiopathic)** **Multiple System Atrophy (MSA): Striatonigral Degeneration, Olivopontocerebellar Atrophy**
TDP-43/FUS "TDP-43opathies"	**FTLD-U (Frontotemporal Lobar Degeneration)** **Amyotrophic Lateral Sclerosis (ALS)**
TRINUCLEOTIDE REPEATS	**Huntington's Disease** **Spinocerebellar Ataxias** **Friedreich's Ataxia** **C9orf72 Repeat Expansion Disease**

*ALZHEIMER'S DISEASE: β-amyloid + Tau (Sporadic Mixed 3R/4R Tauopathy)	
EPIDEMIOLOGY	Most cases are **SPORADIC** & occur **after 60-65 years of age** **Increased risk in DOWN SYNDROME patients** – *this is because the β-amyloid precursor protein is found on Chromosome 21!*
PRESENTATION	Slowly progressive **dementia** preferentially affecting **memory for RECENT events**; Other findings: confusion, poor judgment, language disturbance, hallucinations
CLINICAL COURSE	Slow becomes more severe & eventually incapacitating; Death usually due to inanition, malnutrition, pneumonia
MOLECULAR BIO	Accumulation of **β-amyloid** – Cleavage of precursor by α-secretase, followed by sequential cleavage by β- & γ-secretase → β-amyloid peptide **RARE Familial Early Onset AD**: autosomal dominant **(β-amyloid peptide & Presenilin 1 & 2)** Common polymorphisms affecting the risk of **Late Onset AD**: **APOE4**
GROSS	 **PAN-LOBAR CORTICAL ATROPHY** with narrowing of the gyri & widening of the sulci ***Occipital Lobe is relatively spared!***  **Dilation of the ventricles** due to loss of brain parenchyma: ***hydrocephalus ex vacuo***
PATHOLOGY	*Plaques & tangles are NOT pathognomonic for AD; but the # of plaques & tangles compared to age-matched controls is the basis for diagnosis*  **NEUROFIBRILLARY TANGLES (Tau)**  **SENILE PLAQUE** w/ **β-amyloid** core
TREATMENT	Symptomatic response to **CHOLINESTERASE INHIBITORS or NMDA Receptor Antagonists (Memantine)** Immunization against Aβ peptide γ-secretase inhibitors

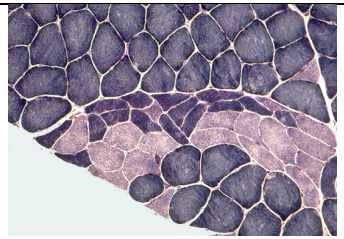
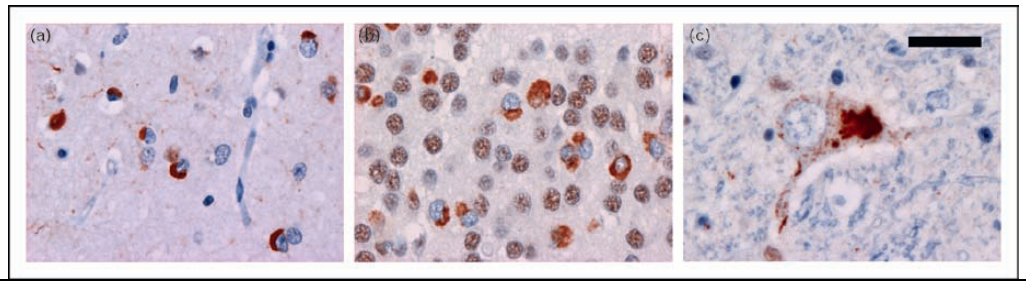
Synucleinopathies: Accumulation of synuclein → FRONTOTEMPORAL DEMENTIA & PARKINSONISM

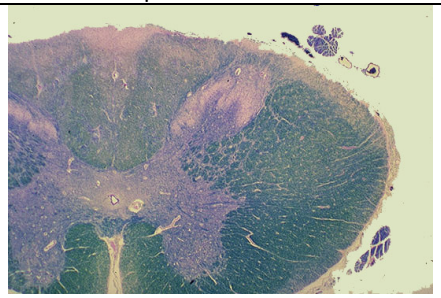
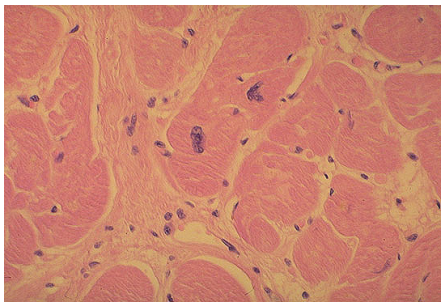
*PARKINSON'S DISEASE: Synuclein aggregates	
PRESENTATION	**RESTING TREMOR ("Pill rolling"), bradykinesia, COGWHEEL RIGIDITY, Stooped posture w/ shuffling gait, Mask-like faces**
CAUSES of PARKINSONISM	**Idiopathic PD – *most common cause*** **Familial Parkinson's** ***POST-ENCEPHALITIC PD:** autoimmune disorder associated with the influenza pandemic of 1919 ***MPTP:** contaminant in heroin that caused an acute, rapidly progressive parkinsonism
MOLECULAR BIO	**PARK1 [AD] (α-synuclein) 4q21:** These patients have **LEWY BODIES**
GROSS	**LOSS OF NEUROMELANIN PIGMENT FROM THE SUBSTANTIA NIGRA &** LOCUS CERULEUS  **NORMAL** **PARKINSON'S DISEASE**
PATHOLOGY	**DEGENERATION OF SUBSTANTIA NIGRA** ***LEWY BODIES:** round, eosinophilic cytoplasmic inclusion made of **α-synuclein** 
TREATMENT	**Sinemet (Carbidopa + Levodopa)**

*HUNTINGTON'S DISEASE: CAG in exons	
DEFINITION	Familial disorder presenting in the **MIDDLE OF LIFE (30-50 y/o),** distinguished by TRIAD: 1. **DOMINANT INHERITANCE** 2. **CHOREA** 3. **DEMENTIA**
PRESENTATION	INSIDIOUS ONSET in a previously healthy patient beginning with **SUBTLE** movement abnormalities (***fidgeting***) or personality changes that eventually become obvious – ***facial grimacing, chorea, dementia***
COURSE	Progresses relentlessly over about 10-15 year course
MOLECULAR BIO	**4p mutation in HUNTINTIN GENE – CAG repeat in exons** Loss of **GABA** neurons & lack of inhibition of VA/VL → ***uncontrollable movement***
GROSS	**DEGENERATION OF CAUDATE, cortical loss, & hydrocephalus ex-vacuo** 

TDP43/FUS-opathies: Accumulation of TDP-43 or FUS → FRONTOTEMPORAL DEMENTIA

- TDP-43 (Transactive response DNA-binding Protein-43): nuclear protein involved in RNA splicing & other parts of RNA metabolism
  - Major pathological protein in Sporadic ALS
  - Most common pathological subtype of FTD – Frontotemporal Lobar Degeneration with Ubiquitinated Inclusions
- FUS: fused in sarcoma
- Genetic mutations in GRN, VCP, CHMP2B, **C9orf72 repeat expansion**

*AMYTROPHIC LATERAL SCLEROSIS	
DEFINITION	**Spontaneous degeneration of UMNs** (Betz cells & axons in the CST) **& LMNs** (anterior horn & cranial motor nerves) ***PRESERVATION OF SENSATION & intellectual function**
PRESENTATION	***Wasting*** (LMN) in the **UPPER EXTREMITIES** ***Spasticity & hyperreflexia*** (UMN) in the **LOWER EXTREMITIES**
COURSE	Death often results form RESPIRATORY FAILURE due to involvement of the cervical cord
MOLECULAR BIO	**SUPEROXIDE DISMUTASE (SOD1)** **C9orf72 REPEAT EXPANSION**
GROSS	**ATROPHY OF VENTRAL SPINAL MOTOR NERVE ROOTS & CRANIAL MOTOR NERVES (LMN degeneration)** **LOSS OF AXONS IN CST (UMN degeneration) → secondary demyelination in Lateral CST (chalky white discoloration)**
PATHOLOGY	 **NEUROPATHIC MYOPATHY:** *Patches of muscle fibers innervated by the same neuron will all atrophy together*  **TDP-43 INCLUSIONS in ALS & FTLD-U** TDP-43 neuronal inclusions in (a) **Neocortex**, (b) Hippocampus in FTLD-U, (c) **LMN** in ALS

FRIEDREICH'S ATAXIA: GAA in intron	
TRIAD	HYPOACTIVE KNEE + ANKLE JERKS + SIGNS OF PROGRESSIVE CEREBELLAR DYSFUNCTION + PRE-ADOLESCENT ONSET
PRESENTATION	PRE-ADOLESCENT ONSET! HYPERREFLEXIA, STAGGERING GAIT, FREQUENT FALLING, PES CAVUS, HAMMERTOES, KYPHOSCOLIOSIS, +BABINSKI, HYPERTROPHIC CARDIOMYOPATHY & CARDIAC FIBROSIS, ↓proprioception & vibration senses
MOLECULAR BIO	Autosomal recessive, GAA repeat in INTRONS → reduced expression of FRATAXIN (9q13) Frataxin is a protein involved in IRON METABOLISM (mitochondrial impairment)
PATHOLOGY	 DEGENERATION OF THE CEREBELLUM, SPINOCEREBELLAR TRACTS, Dorsal columns, Pyramidal tracts  CARDIAC FIBROSIS