DEMYELINATING, DEGENERATIVE AND NEUROPATHIC DISORDERS

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DEMYELINATING DISORDERS

Multiple sclerosis

- The disease generally occurs in young adults (3^{rd}-4^{th} decades); however, 5% of cases are seen in children.
- Females 2:1.
- Risk is high in monozygotic twins (25%);
- fraternal twins and first degree relatives have same risk (15%).
- Epigenetic factors predominate in transmission.
- Increased sun exposure is associated with lower risk for multiple sclerosis.

Multiple sclerosis

- Epstein Barr virus as a causative agent.
- Untreated, life expectancy falls 7-14 years
- Annual loss is 3 times that of normal population
- 20-40%, secondary progression at 10-15 years post onset if untreated

Multiple sclerosis

- Signs and symptoms disseminated in time and space.
- Cortex, justacortex, spinal cord lesions are dissemination in space
- Oligoclonal bands are dissemination in time
- Symptomatic and asymptomatic lesions are dissemination in space and time
- Evoked potentials to diagnose occult optical lesions

Multiple sclerosis

- Tingling and numbness in affected area is an early sign. May precede visual disturbance.
- The usual presentation is diplopia with blurred vision.
- Painful loss of vision may occur (optic neuritis) and residual loss of color vision may result.
- Trigeminal neuralgia in a young person should raise suspicion of Multiple Sclerosis.

Intranuclear ophthalmoplegia

- Reflects a lesion in the ipsilateral medial longitudinal fasciculus.
- The absence of a consensual light reflex places the damage in the optic nerve.
- Weakness of the medial rectus with failure of the opposite eye to adduct on the side of the lesion.
- Nystagmus and weakness of the lateral rectus on the opposite side.

Multiple sclerosis

- Limb weakness develops over time.
- Hyper-reflexia, spasticity noted.
- Impaired position, vibratory, temperature, touch, or pain sense.
- May develop ataxia, dysarthria.
- Presentation with bowel or bladder symptoms (autonomic dysfunction) is indicative of poor prognosis.
- 85-90% of patients relapse.

Four types of multiple sclerosis

- Clinically isolated
- Neurologic symptoms caused by inflammation and demyelination lasting >24 hours
- If no lesion on MRI, low probability of progressing
- If lesion on MRI, high probability of developing relapsing-remitting MS
- May be treated with disease modifying agents

Four types of multiple sclerosis

- Relapsing-remitting
- 85% of patients
- Clearly defined attacks of new or increasing neurologic symptoms followed by periods of partial or complete recovery
- There is no apparent progression of the disease during the periods of remission
- May be either active (with relapses and/or evidence of new MRI activity over a specified period of time) or not active, worsening (a confirmed increase in disability following a relapse) or not worsening
- 90% will have progressed by 20 years

Four types of multiple sclerosis

- Secondary progressive
- Follows an initial relapsing-remitting course
- Transition to a secondary progressive course in which there is a progressive worsening of neurologic function (accumulation of disability) over time.
- Primary Progressive
- Worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions.

Multiple sclerosis

- Early life infections may attenuate responses that lead to autoimmune disease such as multiple sclerosis.
- EBV nuclear antigen (EBNA-2) structurally similar to myelin basic protein.
- Measles virus has also been implicated as an etiologic agent in MS.
- Mutations noted in gene coding for IL-7 receptor, stimulate cell growth.
- HLA-DRB1*15:01 is the most strongly linked factor.

National Multiple Sclerosis Society

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time. See Lancet Neurology paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset	(see KEY below for definitions)
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (**DIS**) and dissemination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional clinical attack implicating different CNS site – **DIS**: ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**

CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria

KEY: **CIS**: clinically isolated syndrome **CNS**: central nervous system **CSF**: cerebrospinal fluid **DIS**: dissemination in space **DIT**: dissemination in time **T2 lesion**: hyperintense lesion on T2-weighted MRI

*Thompson AJ, et al. Lancet Neurol 2017; online Dec 21. http://dx.doi.org/10.1016/S1474-4422(17)30470-2.

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued)	(see KEY on reverse for definitions)
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional attack implicating different CNS site – **DIS**: ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
...in a person with progression of disability from onset	
• progression from onset	– 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: – ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) – ≥2 T2 spinal cord lesions – CSF-specific (i.e. not in serum) oligoclonal bands

The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.

More resources for clinicians: https://www.nationalmssociety.org/For-Professionals/Physicians

McDonald Criteria (2018)

Clinical Presentation	Additional Data Needed
* 2 or more attacks (relapses) * 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
* 2 or more attacks * 1 objective clinical lesion	Dissemination in space, demonstrated by: * MRI * or a positive (cerebrospinal fluid) CSF and 2 or more MRI lesions consistent with MS * or further clinical attack involving different site
* 1 attack * 2 or more objective clinical lesions	Dissemination in time, demonstrated by: * MRI * or second clinical attack
* 1 attack * 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: * MRI * or positive CSF and 2 or more MRI lesions consistent with MS **and** Dissemination in time demonstrated by: * MRI * or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) and Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF

Neuromyelitis optica spectrum disorder

- Mimic MS
- IgG Antibody present to aquaporin 4
- Optic spinal neuromyelitis (Devic's disease)
- More common in those of Asian and African ancestry
- Area postrema syndrome
- Episodic nausea and vomiting or hiccups
- Respond to steroids

Neuromyelitis optica spectrum disorder

- Transverse myelitis
- Aggressive (if not MS)
- Usually involves 3 segments, complete
- Remitting disease in MS (usually partial, 1 segment)
- Responds to steroids
- Plasmapheresis if steroids fail

Multiple sclerosis

- Gross pathology:
- Firm well circumscribed ovoid plaques (Sclerosis)
- Sites:
- Periventricular region
- Corpus callosum
- Basal ganglia.

Histopathology

- Active and relapsing disease
- Early plaques are hypercellular.
- Macrophages are lipid laden.
- Perivenular lymphocyte cuffing.
- Myelin reactive T-cells are found in plaques of multiple sclerosis. (CD4 T_{H1}, T_{H17}, and CD8)
- Axons preserved.
- Diminished numbers of oligodendrogliocytes.
- Neurons spared.

Histopathology

- Progressive multiple sclerosis
- Global inflammation of the brain and meninges
- OR diffuse axonal injury in normal appearing white matter
- OR cortical demyelination affecting the subpial layers of the cerebral cortex.
- Chronic cerebral venous insufficiency highly prevalent in progressive multiple sclerosis
- May represent an effect of injury, not cause.

Multiple sclerosis

- Global inflammation may be confused with acute disseminated encephalomyelitis (following viral or mycoplasma infection);
- However, large numbers of these patients progress to overt multiple sclerosis.

Multiple sclerosis

- Shadow plaques show partial myelination at borders.
- Inactive lesions are hypocellular.
- Myelin is not found.
- Astrocytosis.
- Few oligodendrogliocytes.

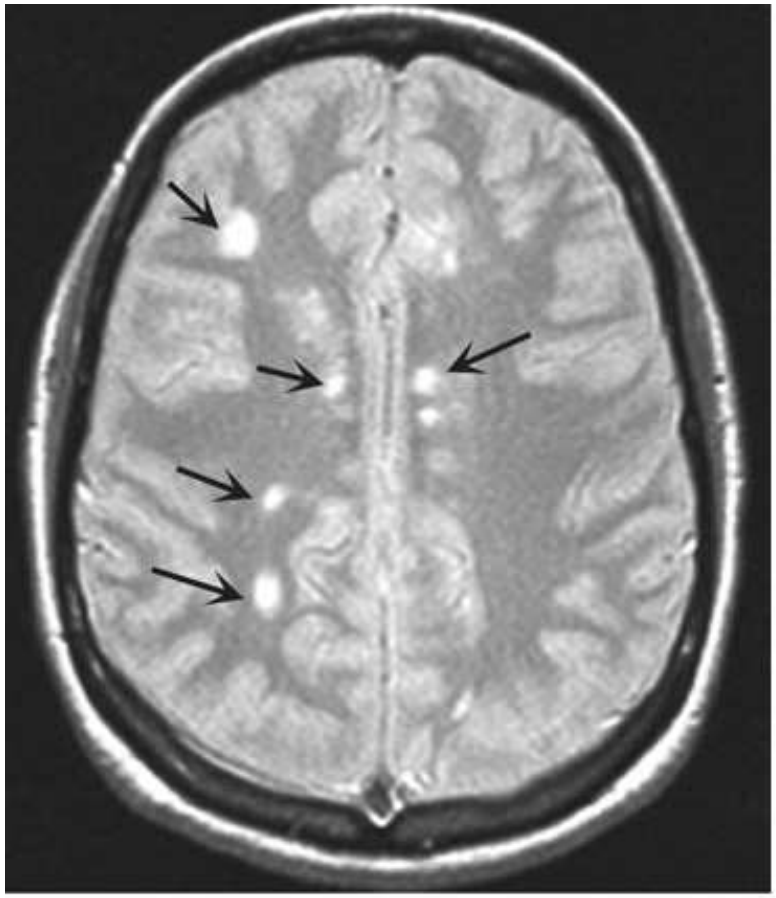
Multiple sclerosis

- Devic disease
- Occurs principally in Asia.
- Presents as bilateral optic neuritis with spinal cord involvement.
- Involves gray matter as well.
- Marburg disease
- Fulminant presentation of multiple sclerosis in young adults.
- Approximately 10% of patients present with rapidly progressive disease

Diagnosis

- Evoked potentials useful
- Demonstrating plaques in optic nerves.
- Demonstrating pontine plaques.
- Two or more oligoclonal bands on cerebrospinal fluid immunoelectrophoresis is diagnostic.
- Presence of Gadolinium enhancing lesion on MRI or nine or more T2 lesions (generally periventricular) and an infratentorial lesion diagnostic of progressive disease.

MRI



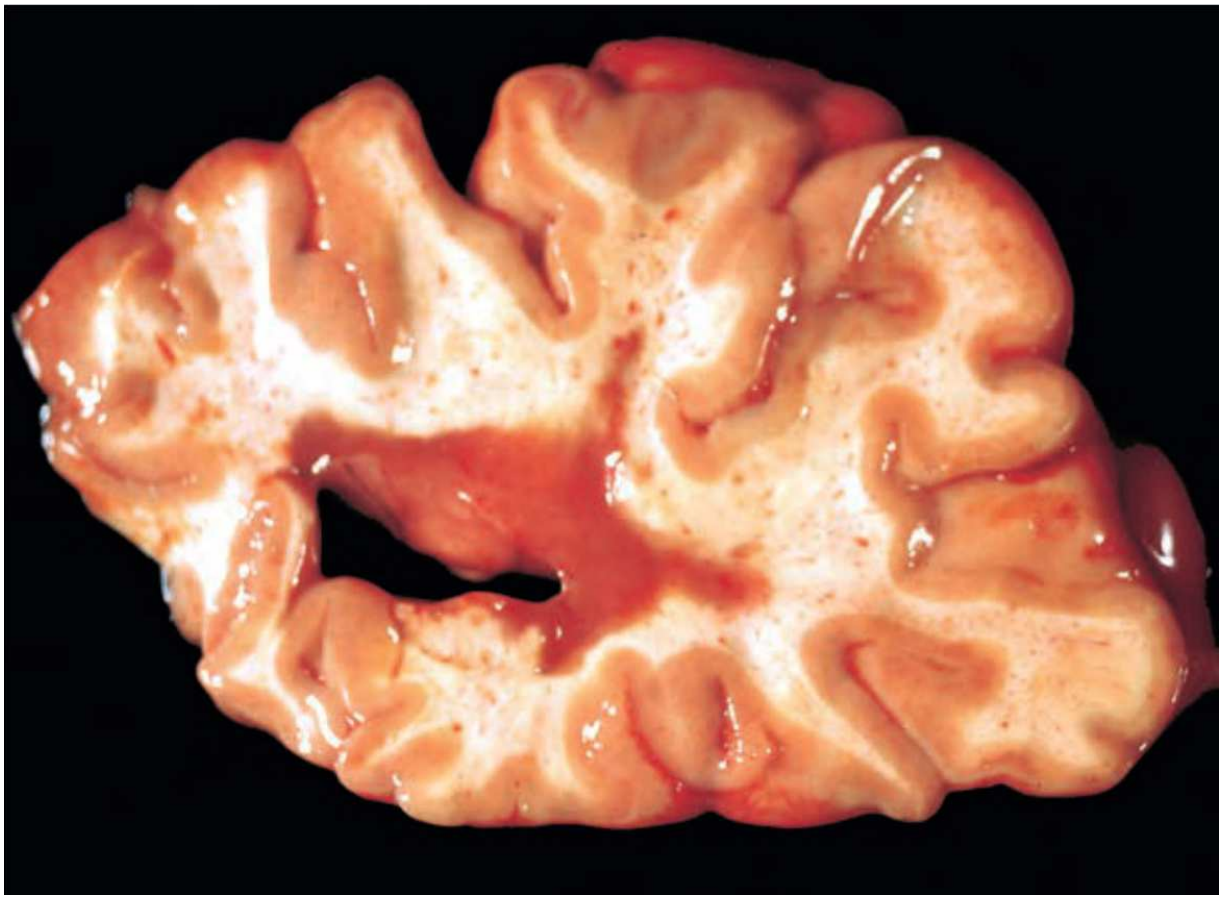
A

Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for multiple sclerosis

Fig. 375-3 Accessed 02/01/2010

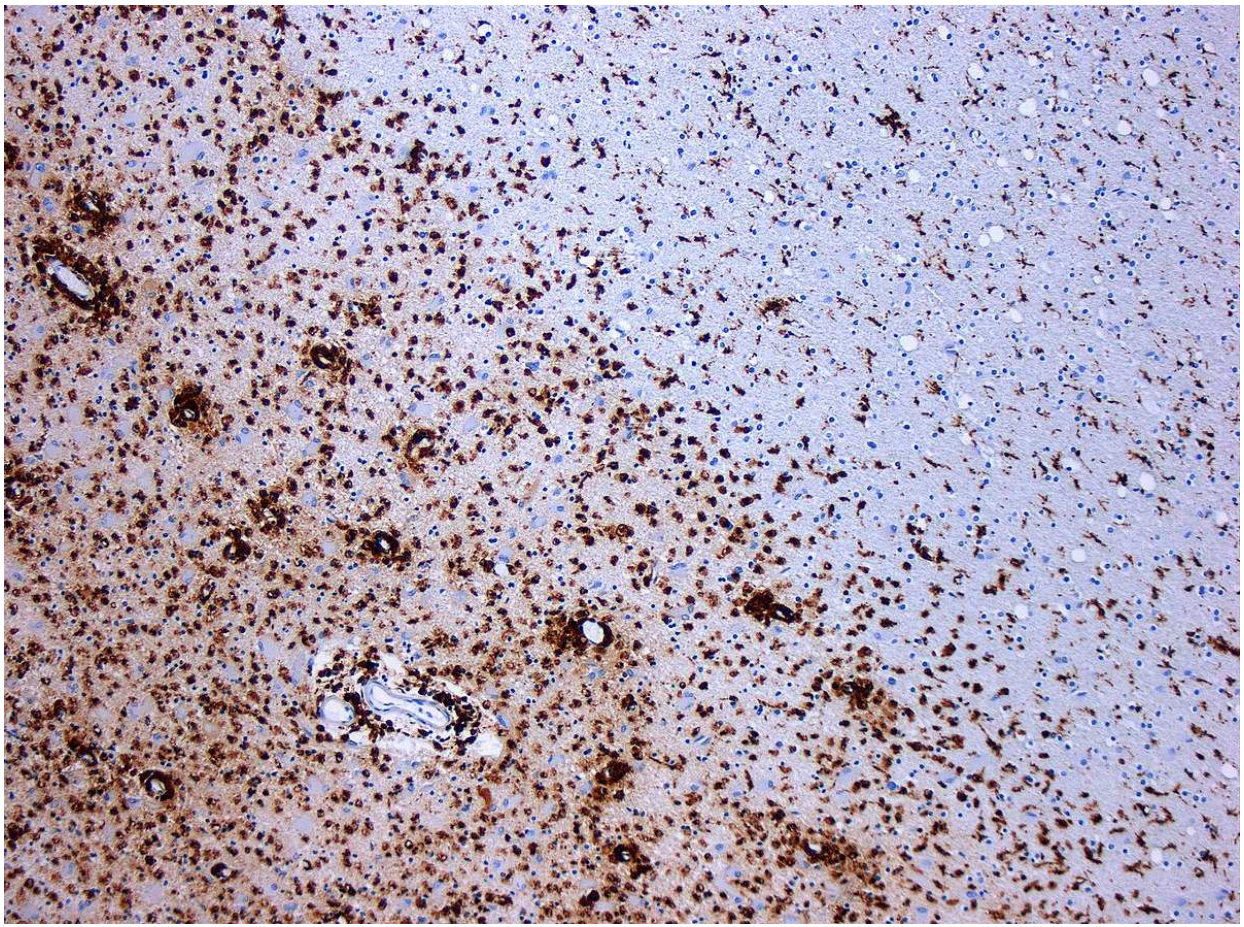
Multiple sclerosis

Lesions are firmer than the surrounding white matter **(sclerosis)** and appear as well circumscribed, somewhat depressed, glassy, gray-tan, irregularly shaped **plaques**. The area of demyelination often has sharply defined borders.



Frosch, MP, Anthony, DC, De Girolami, U, "The Central Nervous System," in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-33 Accessed 10/25/2019

Active demyelinations



https://upload.wikimedia.org/wikipedia/commons/thumb/5/59/MS_Demyelinisation_CD68_10xv2.jpg/1200px-MS_Demyelinisation_CD68_10xv2.jpg

Accessed 12/10/2019

Other demyelinating disorders

- Progressive multifocal leukoencephalopathy
- May present following therapeutic use of antibody to α4-integrins or CD20
- May follow chemotherapy
- Seen in the immunocompromised patient
- It also has an infectious origin.

Other demyelinating disorders

- Severe electrolyte abnormalities may result in central pontine myelinolysis.
- May follow
- General anesthesia
- Liver transplantation
- Alcoholism
- Associated with a rapid correction of low (<120) Sodium levels.

Other demyelinating disorders

- Marchiafava-Bignami disea**se**
- Type A involves the anterior commisure and corpus callosum.
- Upper motor neuron signs as well.
- Stupor predominates
- Type B is milder
- Alcohol abuse and thiamine deficiency

Multiple sclerosis treatment

- Corticosteroids are employed in acute attacks.
- Plasmapheresis also employed in acute attacks.
-
- The only disease modifying drug available for primary progressive disease as well as clinically isolated, relapsing-remitting, and secondary progressive disease is ocrelizumab
-
- Platform drugs for relapsing-remitting disease are β-interferon and glatimer acetate (injectable)

Fingolimod and siponimod reduce relapse rate (oral). Siponomid may also slow progression.

Multiple sclerosis treatment

- Ocrelizumab
- Depletes CD20+ B cells by antibody dependent cell-mediated cytotoxicity
- Depletion persists up to 72 weeks post infusion
- Pre-existing humoral immunity preserved
- Probably crosses placenta (is an immunoglobulin)
- Probably enters into breast milk (is an immunoglobulin)
- Increased risk of viral reactivation (HBV, JC) as well as increased risk of breast cancer

Multiple sclerosis treatment

- Interferon-β given subcutaneously is associated with slowing the progress of disease as well as diminishing disability in relapsing-remitting variant.
- Decreases blood-brain barrier permeability
- Restores T_{reg} cells
- Inhibits antigen presentation
- Little crosses placenta
- Does not pass into breast milk
- Its use leads to a ‘flu like syndrome.
- Most effective therapy in slowing progression to chronic disease

Multiple sclerosis treatment

- Glatiramer acetate
- Myelin like polymer
- Deletes myelin reactive T cells.
- Promotes differentiation in T_H and T_{reg} cells leading to bystander suppression in CNS
- Reduces relapses
- Does not cross placenta
- Does not pass into breast milk
- Post-injection flushing reaction may be severe
- 29% reduction in relapse rate over 24 months

Multiple sclerosis treatment

- Fingolimod and siponimod
- Block sphingosine-1-phosphate receptor
- Block lymphocyte egress from lymph nodes
- Heart block or bradyarrhythmia after first dose
- Associated with serious infections
- Stop 3 months pre-conception
-
- Natalizumab may decrease relapse rate in relapse-remitting variant
- 90% have infusion reaction
- Use may lead to reactivation of JK virus and development of progressive multifocal leucoencephalopathy.

Multiple sclerosis treatment

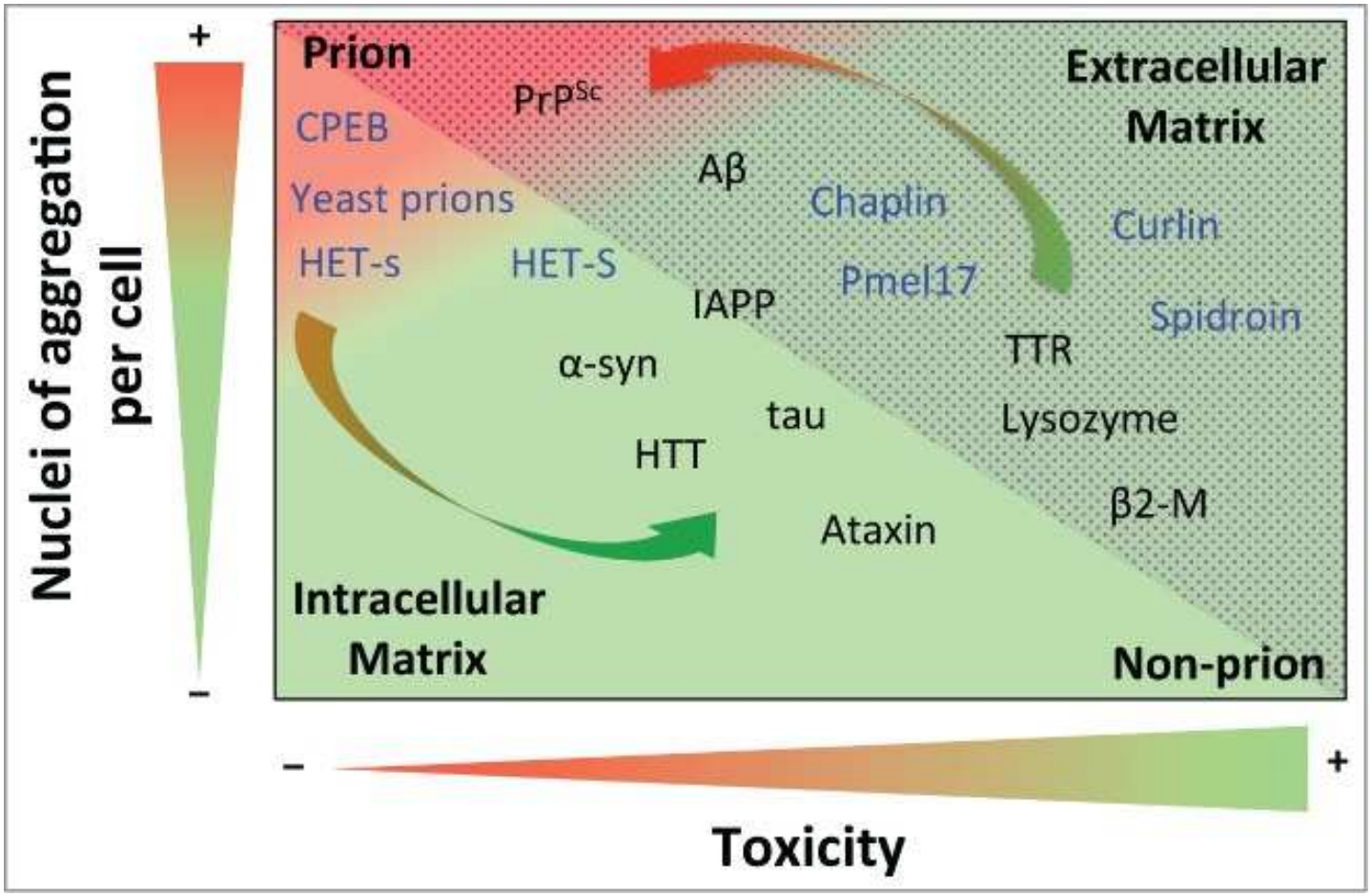
- Cladribine
- Resistant to adenine deamination
- Stop 6 months pre-conception
- 58% decrease in relapse rate at 96 weeks in rapidly progressive disease
-
- Vitamin D supplementation recommended
- High daily doses of Biotin slow progression by activating CoA and pyruvate carboxylases to increase myelin repair and synthesis as well as to generate ATP to limit neurodegeneration

DEGENERATIVE DISORDERS

Degenerative disease

- Each neurodegenerative disease is distinguished by progressive neuronal degeneration in specific reproducible areas of the brain.
- Some lead to progressive dementia;
- others, to specific motor abnormalities.
- Individuals who take anticholinergic drugs or statins have a higher risk of later developing irreversible dementia
- Else, no other inciting events are known to lead to the selective neuronal loss seen.
- May reflect prion process

Prion proteins and infectivity



Sabate, R, "When amyloids become prions," Prion (2014) 8:233-239 doi: 10.4161/19336896.2014.968464 Accessed 12/10/2019

Alzheimer's disease

- Alzheimer Disease is the cause of approximately 50% of the clinical dementias in the elderly.
- 1% prevalence 60-65 years of age.
- Doubles yearly.
- 5-10% familial.
- Autosomal dominant
- Mutations in the APP gene are the most common cause of Alzheimer's disease as well as cerebral amyloid angiopathy.
- Aβ protein is result of APP mutation

Alzheimer's disease

- The Aβ portion of the transmembrane APP extends from the extracellular region into the transmembrane domain.
- If cleaved at the cell surface by α-secretase, and then cleaved within the membrane by γ-secretase, a soluble fragment is created (soluble β-amyloid)
- If cleaved at the cell surface by β-secretase, and then cleaved within the membrane by γ-secretase, the portion may be paired with one cleaved by α-secretase and form the Aβ-peptide.

Alzheimer's disease

- $A\beta_{40}$ and $A\beta_{42}$ are abnormal monomers that result
- This form is highly prone to aggregation.
- The peptide is directly neurotoxic (β-amyloid).
- Initially phagocytized;
- However, microglia are chronically activated and secrete IL-1, IL-6, and TNF
- Microglial receptors for advanced glycation end products also bind Aβ peptide, further amplifying cytokine production

Aβ

- Vascular dysfunction caused by cerebral amyloid angiopathy reduces perivascular Aβ clearance
- Aβ accumulates
- Factors that favor vascular Aβ deposition over parenchymal deposition include:
- $Aβ_{40}$ (termination of Aβ at or before position 41)
- Missense mutations within the Aβ coding region
- Co-deposited proteins, such as fibrinogen.

Alzheimer's disease

- Soluble β-amyloid binds to the receptor found on both immune cells and neurons (LilrB) .
- The bound complex activates cofilin which begins to degrade actin and leads to synapse disassembly.
- LilrB is a means to check synapse strengthening
- Insoluble β-amyloid protein accumulates in neurons, glial cells, and vessel walls.
- BUT, 30% of patients do not have amyloid.
- AND many "normals" who have amyloid do not have dementia.

APP gene

- Amyloid-β (Aβ) in the brain interstitial fluid can be cleared via perivascular drainage pathways or deposited as neuritic plaques in the brain parenchyma or as cerebral amyloid angiopathy along vessel walls.
- A picture of progressive dementia is also seen in Down's syndrome.
- APP gene at 21q21.3

Alzheimer's disease

- PSENEN at 19q13.2
- Encodes ApoE (γ-secretase enzyme)
- Gain of function mutations in <u>early onset form</u>
- The dosage of allele ε4 increases risk and lowers age of onset; that at ε2 is associated with delayed onset.
- <u>Apolipoprotein is also a potential prion protein</u>

Alzheimer's disease

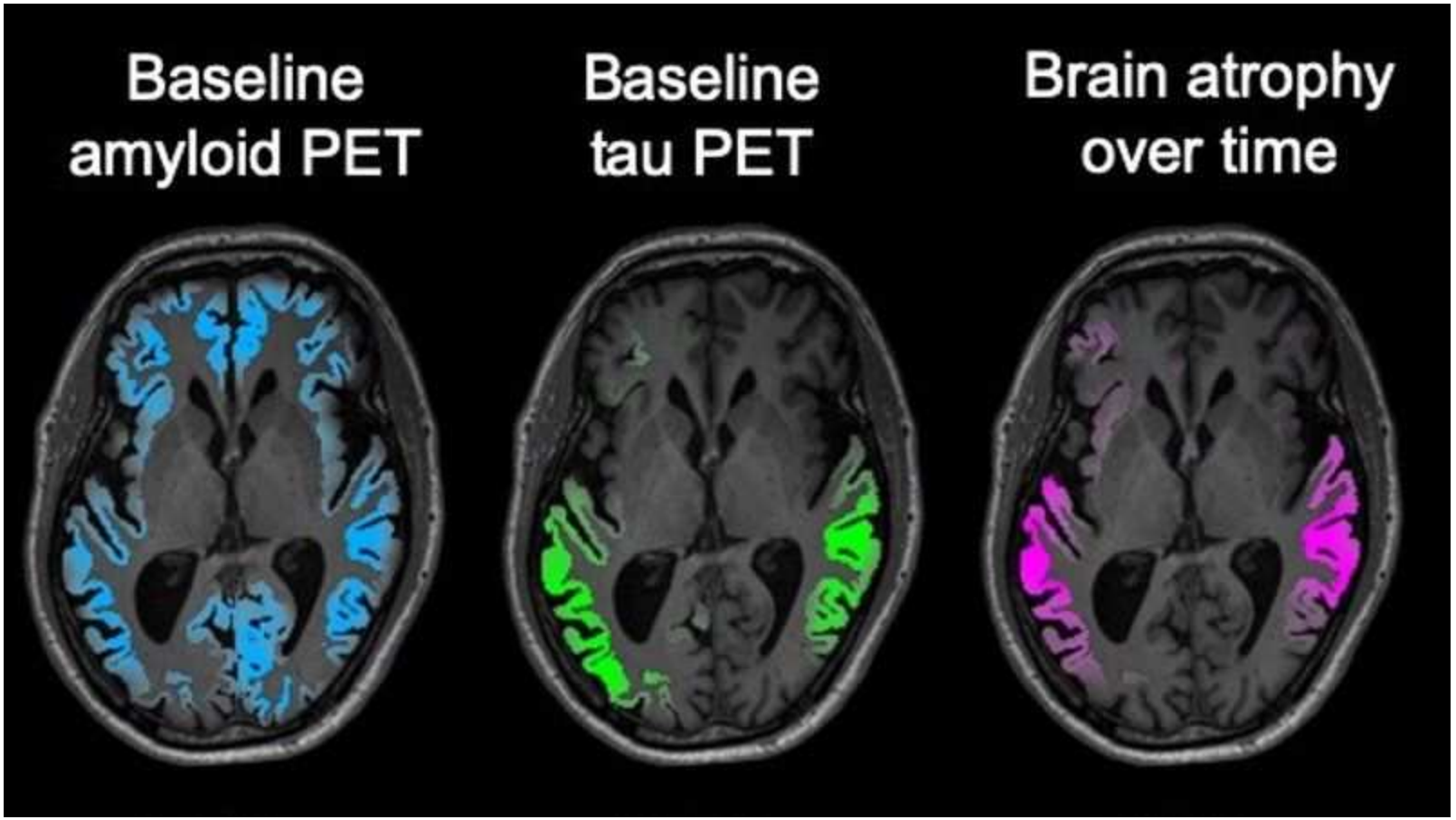
- Tau proteins are heat stable, soluble products of MAPT gene at 17q21.31
- Six isoforms; three with 3 repeated segments; four with 4 repeated segments
- Balance of isoforms needed for normal function
- Maintain microtubule structure
- Tau proteins may hyperphosphorylate, clump, and migrate independently. Are potential prion proteins
- Blocks capsase and proteosome clearing of misfolded proteins.
- Aggregates are found in 25% of dementia cases.
- Cause neurofibrillary tangles.

Alzheimer's disease

- Drives brain degeneration in Alzheimer's more than does amyloid protein
- Predicts further atrophic changes and sites
- No effective therapy

- GFAP, NEFL, GDF15 and LTBP2 associated with dementia

- 25% of dementia is multi-infarct



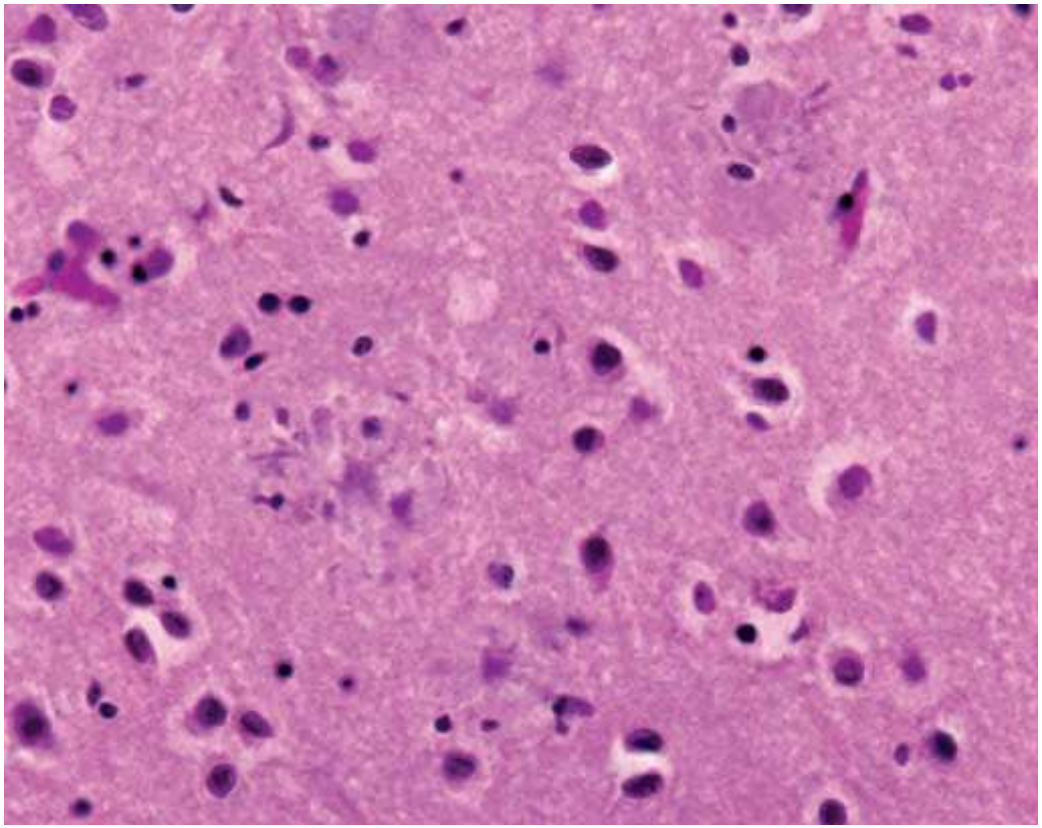
Tau PET brain scans (green) in early clinical-stage Alzheimer's patients accurately predict the location of brain atrophy measured by MRI 1–2 years later (magenta). Amyloid PET imaging (blue) does not predict the location of either tau or future brain atrophy.

Alzheimer's disease

- Cortical atrophy.
- Characteristic histopathologic changes:
- Neuritic plaques, characterized by dystrophic neurites surrounding an amyloid core;
- Neurofibrillary tangles, cytoplasmic filamentous bundles (tau proteins) that displace or surround the nucleus; and
- Amyloid angiopathy particularly in the hippocampus and olfactory bulb
- Hirano bodies are elongated, eosinophilic, beaded actin containing filaments found within pyramidal cells of the hippocampus.

Alzheimer's disease

Plaques with dystrophic neurites surrounding amyloid cores are visible



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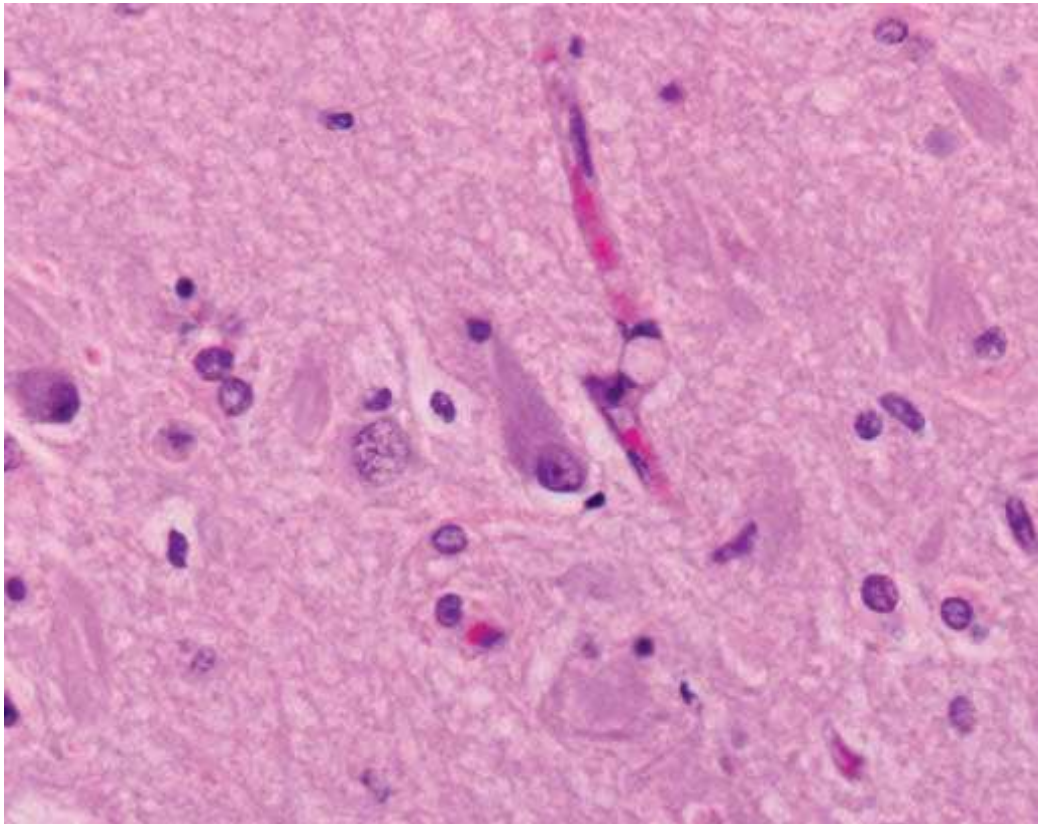
Alzheimer's disease

Neurofibrillary tangle is present within one neuron, and several extracellular tangles are also present



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Tau proteins

- All degenerative diseases with tau proteins share similar mechanism of degeneration.
- Tau proteins induce cell cycle re-entry of post-mitotic neurons.
- Re-entry failure leads to degeneration and death.
- Amyloid deposits or neurofibrillary tangles are a “protective” response as they serve as a “sink” in which abnormal proteins are collected and harm is limited.

Frontotemporal dementias

- Pick disease (FTD-tau)
- Difficult to distinguish from Alzheimer's.
- Occurs in midlife.
- Initially unilateral (fronto-temporal).
- Late, cortical atrophy.
- Inclusions contain 3R tau and argentophilic densely aggregated paired helical filaments (Pick bodies).
- In contrast to Alzheimer's these inclusions do not remain following cell death.

Frontotemporal dementias

- Progressive supranuclear palsy
- Men in their fifth decade
- Associated with extensive neuron loss in the globus pallidus, subthalamic nucleus, substantia nigra, colliculi, periacqueductal gray matter, and the dentate nucleus of the cerebellum.
- Ophthalmoplegia
- Neurofibrillary tangles are straight filaments of 4R tau proteins.

Frontotemporal dementias

- Corticobasal degeneration
- Associated with cortical atrophy, principally in the motor areas.
- 4R tau proteins are identified in astrocytes, oligodendrocytes, basal ganglia neurons, and cortical neurons.
- Clusters of tau proteins around an astrocyte (astrocyte plaque) and their presence as filaments in white and gray matter are characteristic.

Frontotemporal dementias

- FTD-Parkinson-17
- 40-50 years of age
- Loss of inhibition
- Inappropriate emotional responses
- Neglect personal hygiene
- Not interested in events or activities
- Cognitive deficit
- May present with obsessive-compulsive behaviors
- Hallucinate
- Semantic paraphrasia

Frontotemporal dementias

- Parkinson-like symptoms progress over time
- Paralysis of upward gaze
- Saccades
- Autosomal dominant
- MAPT gene mutation
- Tau protein

Frontotemporal dementias

- FTD-TDP43
- Autosomal dominant
- Does not contain tau proteins.
- TAR-DBP gene at 1p36.22
- RNA, DNA repair impeded
- Represent GRN (granulin) mutation at 17q21.31.
- Affects neuronal survival
- Loss of granulin leads to accumulation of TDP-43 proteins
- Aggregates are toxic

Features of dementia

History	
Unprotected sexual intercourse, intravenous drug abuse, hemophilia, or blood transfusions	HIV-associated dementia
Family history	Huntington disease, Wilson disease
Headache	Brain tumor, chronic subdural hematoma
Vital signs	
Hypothermia	Hypothyroidism
Hypertension	Vascular dementia
Hypotension	Hypothyroidism

Features of dementia

General examination	
Meningismus	**Chronic meningitis**
Jaundice	**Acquired hepatocerebral degeneration**
Cranial nerves	
Papilledema	**Brain tumor, chronic subdural hematoma**
Argyll Robertson pupils	**Neurosyphillis**
Ophthalmoplegia	**Progressive supranuclear palsy**
Pseudobulbar palsy	**Vascular dementia, progressive supranuclear palsy**

Features of dementia

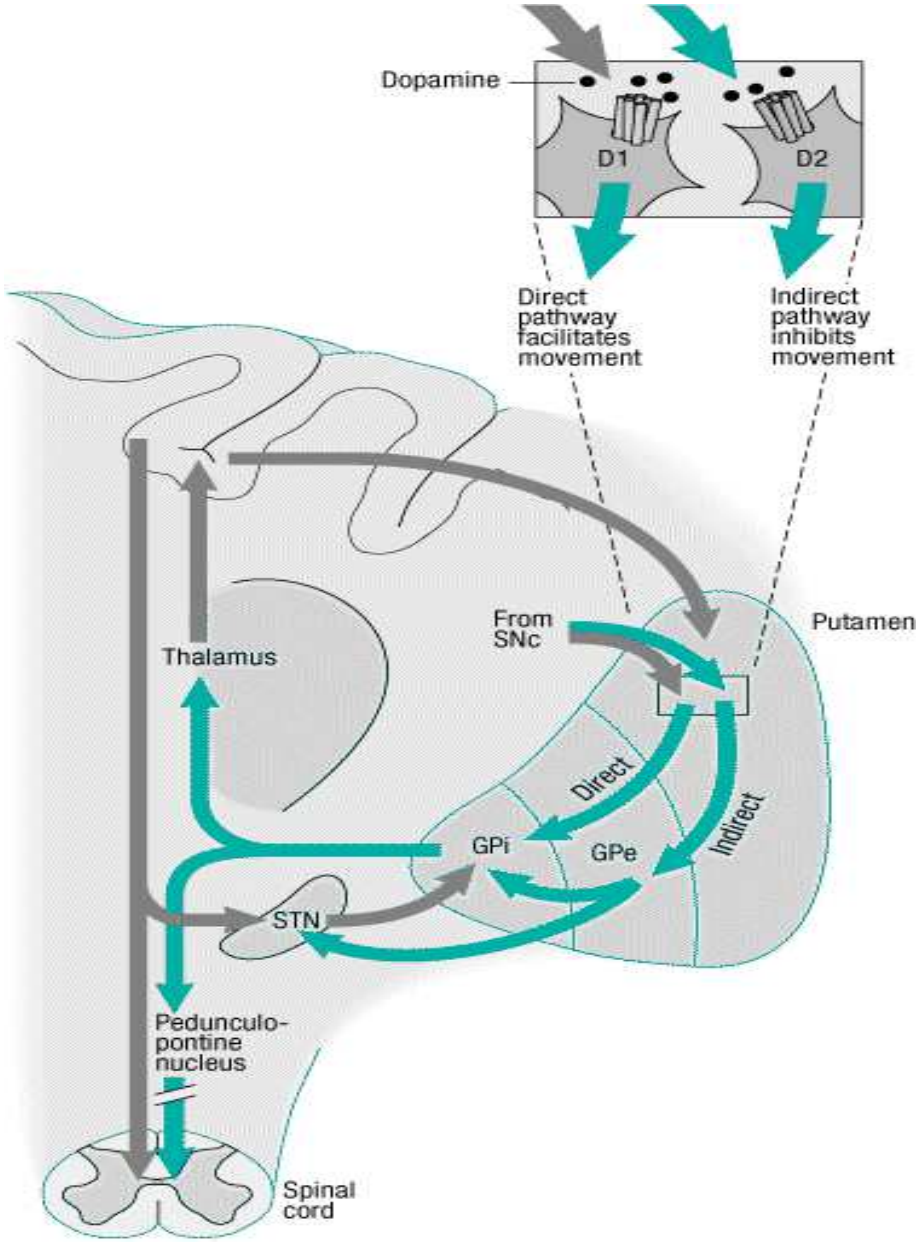
Motor	
Tremor	**Dementia with Lewy bodies, corticobasal ganglionic degeneration, acquired hepatocerebral degeneration, Wilson disease, HIV-associated dementia**
Asterixis	**Acquired hepatocerebral degeneration**
Myoclonus	**Creutzfeldt-Jakob disease, HIV-associated dementia**
Rigidity	**Dementia with Lewy bodies, corticobasal ganglionic degeneration, acquired hepatocerebral degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Wilson disease**
Chorea	**Huntington disease, Wilson disease**
Other	
Gait apraxia	**Normal pressure hydrocephalus**
Polyneuropathy with hyporeflexia	**Neurosyphillis, vitamin B_{12} deficiency, HIV-associated dementia**

Dementia or depression

Dementia	Depression
Indifferent to memory impairment. Semantic paraphasia.	Can describe memory impairment precisely and in detail
Cognitive deficit	No or minimal cognitive deficit
Signs of depression secondary	Brooding, anxiety, sleep disturbance, loss of appetite, self doubt at presentation
Rarely past history of depression	Usually past history of depression

Parkinson's disease

- 20% have dementia.
- Peak incidence 6^{th}-8^{th} decades.
- Associated with loss of dopamine containing neurons and the presence of gliosis.
- Disinhibition of gluatamergic neurons in subthalamus
- Activation of striatal neurons ceases
- Manifest as excessive inhibition of GABAergic neurons of the thalamus
- Voluntary movement is suppressed (hypokinesia)
- Muscle tone is increased (rigor)



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

The blue lines indicate neurons with excitatory effects, whereas the black lines indicate inhibitory influences.

(Reproduced with permission from Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, 4th ed. New York: McGraw-Hill, 2000.)

Fig. 4-3 Accessed 07/01/2010

Parkinson's disease

- Early symptoms include:
- Soft voice (monotonous speech is later development)
- Difficulty with tasks such as turning in bed, opening jars, or rising from a chair
- Bradykinesia
- Micrographia
- Thrashing about during sleep

Parkinson's disease

- Late symptoms include:
- Rigidity of face and trunk
- Resting tremor ("pill rolling)…not constant
- Bent posture
- Excessive sweating and salivary flow
- Depression

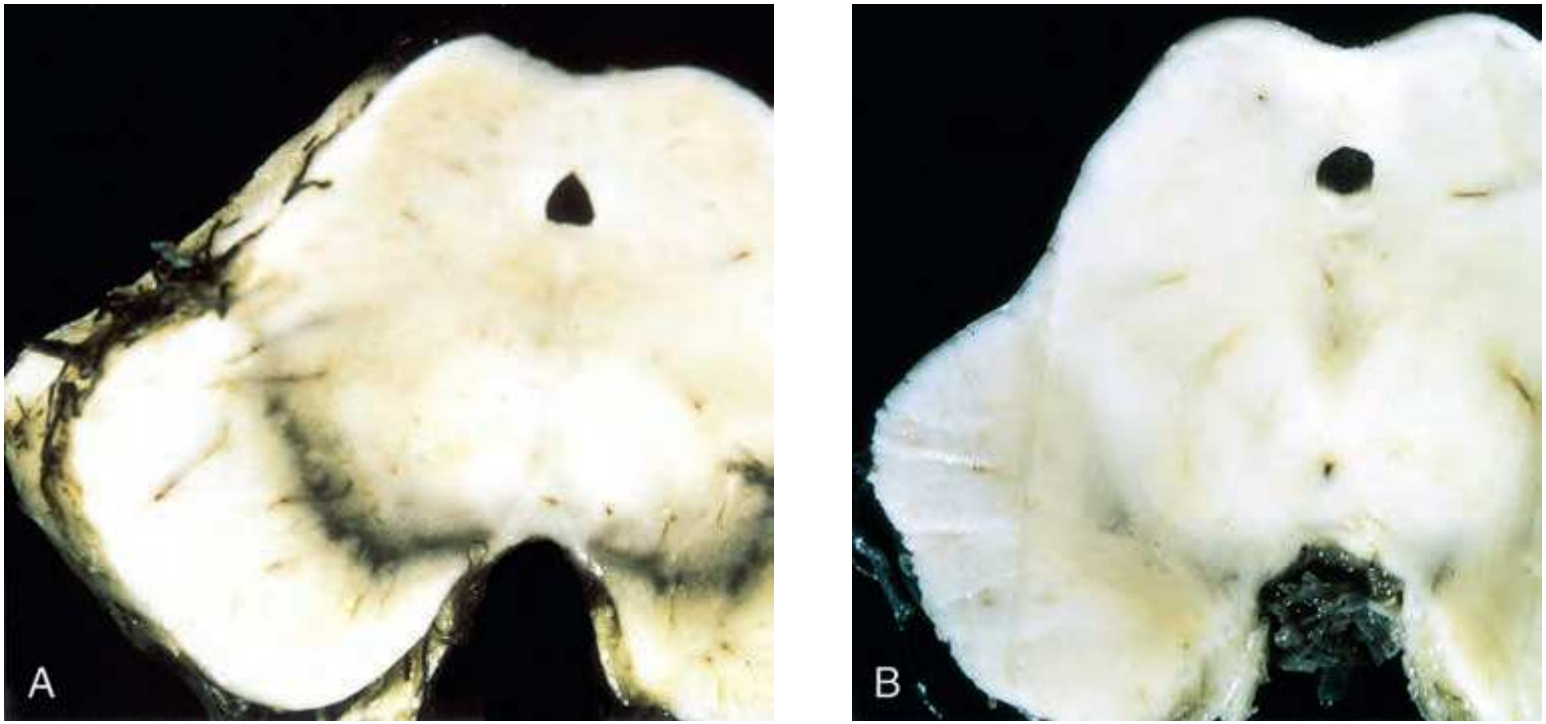
Parkinson's disease

- Common symptoms in Parkinson's disease include tremor (positive likelihood ratio, LR+, 1.5; LR- 0.5), rigidity (LR+ 2.8, LR- 0.4), and micrographia. Bradykinesia and rigidity have an LR+ of 4.5 and an LR- of 0.12.
- The glabella tap (leads to persistent blinking) and heel-to-toe tests are the most useful clinical findings. LR+ 4.5 and 2.9, LR- 0.1 and 0.3, respectively.

Parkinson's disease

- Substantia nigra pallor characteristic.
- Eosinophilic inclusions of fine filaments of α-synuclein (Lewy bodies) are demonstrated microscopically.
- May be found particularly in:
- The cholinergic cells of the basal nucleus of Meynert
- The locus ceruleus
- The dorsal motor nucleus of the vagus.

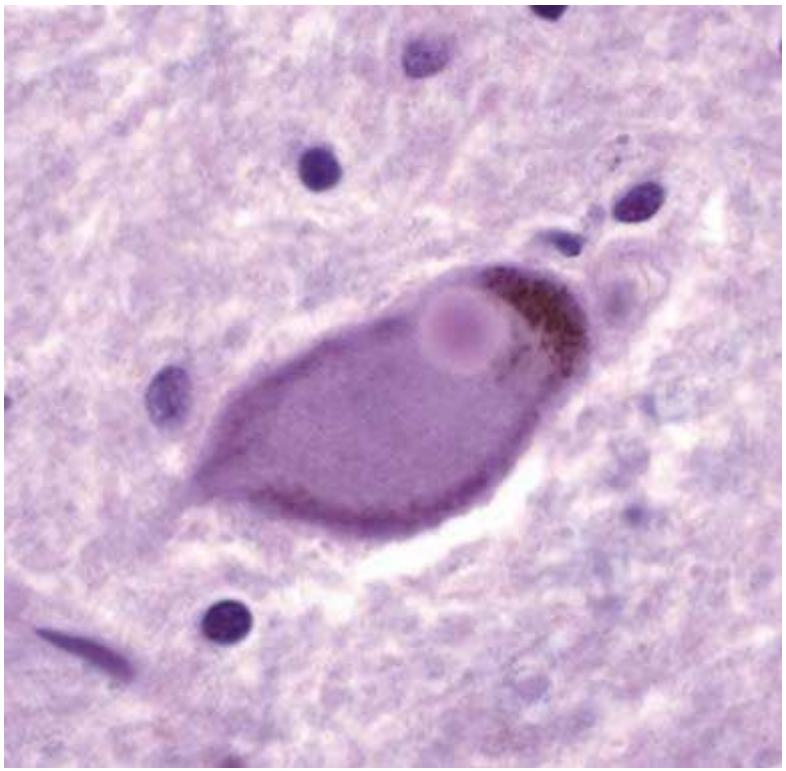
Parkinson's disease



There is pallor of the substantia nigra and locus ceruleus, which is due to loss of the pigmented, catecholaminergic neurons in these regions. Compare A, normal, with B, Parkinson's.

Frosch, MP, Anthony, DC, De Girolami, U, "The Central Nervous System," in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-40A,B Accessed 10/25/2019

Lewy body



Frosch, MP, Anthony, DC, De Girolami, U, “The Central Nervous System,” in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-40C Accessed 10/25/2019

Molecular changes

- LRRK2 (Leucine rich repeat kinase 2) at 12q12
- Dardarin protein encodes an ankyrin found both in cytoplasm and in the mitochondrial outer membrane.
- Interacts with parkin (PRKN) and ubiquitin carboxy terminal hydroxylase 1 (UCH-L1)
- Autophagy
- Kinase activity
- Common association with tremor
- Autosomal dominant (Parkinson's disease 8)
- Found in up to 15% of cases of familial Parkinson's disease and 3% of sporadic cases.

Molecular changes

- SNCA (α-synuclein) amplifications at 4q21 have been found in 2% of familial cases.
- Dose related
- Inhibits phospholipase D2 (as does β-synuclein), affecting dopamine release.

Parkinson's disease

- Large numbers of cases described in survivors of the swine influenza epidemic of 1918 (Von Economo encephalitis).
- May also be precipitated by toxin intake (MTMP).
- Oxidative damage (catecholamine induced) during melanin formation injures substantia nigra neurons.
- May be associated with loss of mitochondrial targeting (DJ1 at 1p36.23 and PINK1 at 1p36.12).

Lewy body

- Up to 15% of patients with Parkinson's disease develop dementia.
- The major correlate is the widespread presence of Lewy bodies.
- Presents first with sleep disturbance
- May see explosive behavior (executive control)
- Dementia
- Parkinsononian symptoms
- Diffuse Lewy body disease may represent an extreme in the continuum of Parkinson's disease.

Parkinson's disease treatment

- L-dopa effective therapy in early disease to mitigate motor symptoms.
- L-dopa passes the blood brain barrier and is converted to dopamine by dopamine carboxylase
- The peripheral metabolism of L-dopa is associated with gastrointestinal disturbances and cardiac arrhythmias.
- Carbidopa inhibits L-dopa degradation and permits lower doses of L-dopa to be employed.
- Choreoathetosis of face and fingers presents over time with L-dopa use.
- Fluctuations in efficacy occur over time.

Parkinson's disease treatment

- MAO-B inhibitors (selective metabolism of dopamine) and COMT inhibitors enhance function in combination with L-dopa.
- Used in those whose response to L-dopa fluctuates.
- COMT converts L-dopa to 3-O-methyldopa in periphery
- COMT competes with L-dopa for entry into the central nervous system)
- Vitamin B6 enhances peripheral metabolism of L-dopa.

Parkinson’s disease treatment

- Gait and tremor symptoms may be ameliorated by acetylcholine (Ach) inhibitors but there is little effect on bradykinesia.
- Ach inhibitors affect pedunculo-pontine nucleus
- Deep brain stimulation may provide relief of motor symptoms.
- Focal ultrasound ablation of globus pallidus may improve motor symptoms.

Multiple system atrophy

- Two variants
  - Both present with autonomic dysfunction
    - Orthostatic hypotension common
    - Once known as Shy-Drager disease
  - Parkinsonian variant
- Striatonigral degeneration
- Less severe changes in substantia nigra and locus ceruleus.
- Olivopontocerebellar atrophy variant
- Ataxia a prominent sign

Multiple system atrophy

- SCNA mutation in those of European descent
- α-Synuclein found in oligodendroglial cells
- α-Synuclein found in presynaptic neurons
- Thought to involve synaptic vesicle formation
- Maintain microtubular structures as well
- COQ2 mutation found in those of Japanese descent
- Inability to produce Coenzyme Q10
-
- Fatal within 7-10 years after diagnosis.

Basal ganglia lesions

Lesioned Area	Effect
Globus Pallidus	Athetosis of hand, an arm, neck , or face
Subthalamic Nucleus	Hemiballismus
Putamen	Flicking movements of hands, face or other body parts (chorea)
Caudate and Putamen	Huntington’s Chorea
Substantia Nigra	Parkinson’s Disease

Huntington's chorea

- 4^{th}-5^{th} decade onset.
- There is a juvenile form
- Most common disease of basal ganglia
- Presenting signs: Depression and irritability
- Involuntary small movements
- Poor coordination
- Impaired learning
- Motor disorder precedes cognitive deficit.

Huntington's chorea

- Autosomal dominant
- HTT gene at 4p16.3
- CAG repeats for polyglutamine.
- The more repeats, the earlier disease onset.
- Threshold effect
- Glutamine stimulates Ca^{2+} uptake into neurons, leading to cell death.
- Striatal neurons affected
- Increase inhibition of GABAergic neurons in subthalamic nucleus.
- Disinhibits neurons in thalamus
- Chorea

Huntington's chorea

- Pathologic changes in the striatum develop in a medial-to-lateral direction in the caudate and from dorsal to ventral in the putamen.
- Marked fibrillary gliosis.
- Caudate atrophy on MRI.
- Tetrabenazine effective as it depletes dopamine.
- 10-15 year survival following diagnosis

Tardive dyskinesia

- Usually head and neck muscles (mainly mouth and tongue), back muscles.
- Brought on by the use of antipsychotic drugs or metoclopropamide and persists after the drugs are discontinued.
- First generation (“typical”) antipsychotics more likely to cause problems than are the second generation (“atypical”) antipsychotics.
- Clozapine only antipsychotic proven to have low probability of tardive dyskinesia adverse reaction.

Tardive dyskinesia

- Drug treatment results in hypersensitivity at the D_2 dopamine receptor. Results in an imbalance in nigrostriatal influence.
- Pretreatment with dopamine depleting agents, benzodiazepines, anti-Parkinsonian agents increases risk.

- Sydenham chorea is associated with rheumatic disease and is reversible.
- Immune complexes deposited in striatum

Freidrich's ataxia

- Most common inherited form of spinocerebellar ataxia (there are 30 types).
- Autosomal recessive.
- Onset between ages 15 and 25.
- 25% may present after the age of 25 (Late Onset)
- If presents after 40, is Very Late Onset
- European, Middle-Eastern, North African peoples
- Hallmark is ataxia of both upper and lower limbs.

Freidrich's ataxia

- Histopathology:
- Loss of axons and gliosis
- Posterior columns
- Distal portion of the corticospinal tracts
- Distal portion of the spinocerebellar tracts.
- Neuronal degeneration
- Clarke's column of the spinal cord
- Brainstem (CN VII, X, XII)
- Dentate nucleus and vermis of cerebellum
- Betz cells of the motor cortex.

Friedrich's ataxia

- May see scoliosis, pes cavus.
- Hypertrophic cardiomyopathy and diabetes mellitus are common associations.
- FXN gene at 9q21.11 with GAA repeat expansion.
- Lack of frataxin protein production affects mitochondrial function by blocking assembly of iron-sulfide complexes.

Ataxia-Telangectasia

- Autosomal recessive.
- Presents before age 5.
- Fatal by early 20’s.
- Ataxia
- Incoordination
- Myoclonus
- Slurred speech
- Difficulty feeding

Ataxia-Telangectasia

- Telangiectatic lesions in:
- CNS
- Cojunctiva
- Skin
- Thymus and lymph nodes hypoplastic
- Primary immunodeficiency disease
- Gonads hypoplastic.
- Very sensitive to ionizing radiation.
- ATM gene at 11q22.3 (difficulty repairing double stranded DNA breaks).

Ataxia-Telangectasia

- Histopathology:
- Loss of Purkinje cells and granule cells in cerebellum.
- Degeneration in:
- Dorsal columns
- Spinocerebellar tracts
- Anterior horn cells
- Peripheral neuropathy
- Schwann cells in dorsal root ganglia and peripheral nerves are enlarged
- Endothelial cells enlarged
- Pituicytes enlarged.

Amyotrophic lateral sclerosis

- Men predominate.
- 5th decade.
- There is a juvenile form.
- Up to 90% are sporadic
- Begins with muscle wasting.
- Fasciculations may be seen.
- Dysarthria
- Dysphagia
- Hyperreflexia
- Demonstration of upper motor neuron disease in three regions of the body is diagnostic.
- 20% will develop frontotemporal dementia

Amyotrophic lateral sclerosis

- Histopathology:
- Loss of neurons (Betz cells) in the primary motor cortex
- Loss of motor nuclei in the brainstem
- Loss of upper motor neurons leads to hyperreflexia
- Loss of neurons in the anterior horn of the spinal cord.
- Microgliosis is associated.
- Loss of lower motor neurons leads to neurogenic muscular atrophy.
- Demyelination of the corticospinal tract.

Amyotrophic lateral sclerosis

- Familial cases are generally autosomal dominant
- Up to 40% are associated with Corf72 mutation at 9p21.2 (GGGGCC repeats)
- Affects RNA synthesis.
- Frontotemporal dementia
- Up to 25% associated with SOD1 (superoxide dismutase gene 21q22.11)
- Protein misfolding

AV4 mis-sense mutation of SOD1 associated with rapid course and lack of upper motor neuron signs.

Amyotrophic lateral sclerosis

- 5% are associated with FUS gene at 16p11.2
- FUS governs RNA transcription
- 5% with TARDBP at 1p36.22
- TAR DNA binding protein governs RNA and DNA transcription
- KIF5A gene at 12q13.3

Microtubule motor transport function (slow axonal transport) impaired

- ALSN gene at 2q33-35
- Alsin is a structural homologue of proteins involved in GTPase regulation and endosomal trafficking.

Amyotrophic lateral sclerosis

- Sporadic cases may be an unrecognized autosomal recessive pattern of inheritance

- X-linked dominance has also been described. UBQLN2 (ubiquilin-2) at Xp11.21
- Motor neurons may contain eosinophilic bodies and ubiquitin–rich aggregates.

- Antibody to GM1 is a common finding.

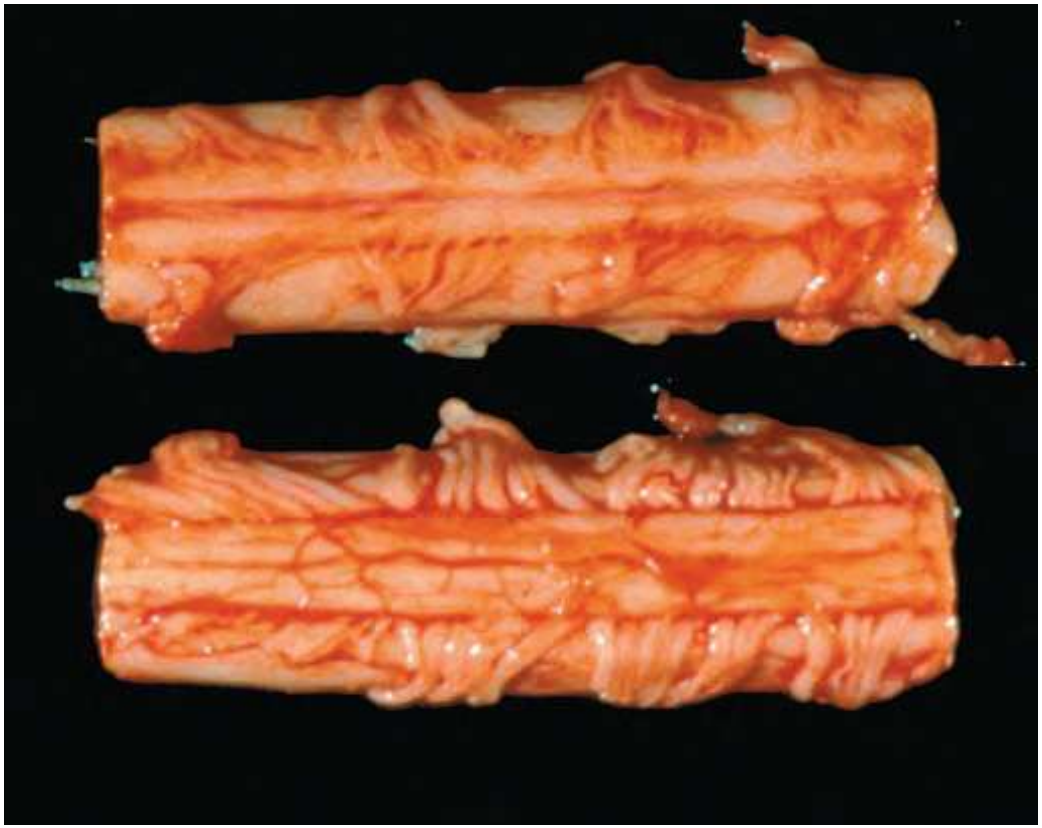
- Inhibition of the neurotransmitter glutamate has lead to some clinical improvement.

Amyotrophic lateral sclerosis

- Neurodegenerative tauopathy variant
- Rich in tau neurofibrillary tangles
- Chamoro people in Guam
- Kii people of Japan
- Parkinson-like syndromes and dementia are associated with this entity
- Spatial functions lost first
- Cognitive changes follow
- Related to ingestion of a cyanobacteria produced metabolite resembling β-alanine that leads to glutamate release and is neurotoxic

Amyotrophic lateral sclerosis

Segment of spinal cord viewed from anterior (upper) and posterior (lower) surfaces showing attenuation of anterior (motor) roots compared with posterior (sensory) roots.



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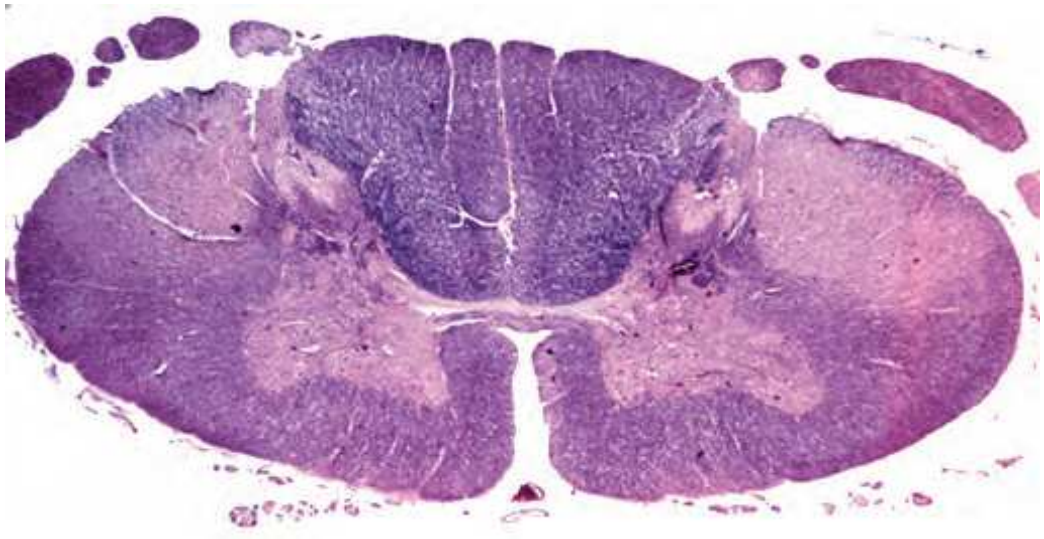
Amyotrophic lateral sclerosis



Spinal cord showing loss of myelinated fibers (lack of stain) in corticospinal tracts as well as degeneration of anterior roots.

Frosch, MP, Anthony, DC, De Girolami, U, “The Central Nervous System,” in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-43B Accessed 10/25/2019

NEUROPATHIES

Neuropathies

Disease	Signs and symptoms	Treatment
Guillan-Barré (acute inflammatory demyelination)	Ascending level of weakness. Often associated with antecedent viral illness, immunization, Mycoplasma pneumoniae or Campylobacter infection. Elevated CSF protein.	Intravenous immunoglobulin beneficial early. Plasmapheresis if circulating antibody (to myelin).
Chronic inflammatory demyelinating polyneuropathy	>40 years old with both weakness and painless sensory deficits. Slow conduction on EMG (axonal degeneration).	Corticosteroids. Possibly intravenous immunoglobulins or plasmapheresis.
Multifocal motor neuropathy	Progressive, symmetric weakness of distal muscles with areflexia. Sensation spared. Conduction block of motor nerves on EMG.	Intravenous immunoglobulins; later, cyclophosphamide
Paraprotein	Usually monoclonal gammopathy. May see IgM autoantibodies that bind myelin-associated glycoprotein.	Plasmapheresis

Neuropathy syndromes

- Predominantly symmetrical motor deficits
- ALS, Guillan-Barré, chronic inflammatory demyelinating polyneuropathy, acute porphyria
- Predominantly asymmetrical or focal motor deficits
- Neuropathy such as ALS, poliomyelitis, spinal muscular atrophy
- Radiculopathy or plexus lesion
- Mononeuropathy such as compartment syndrome or lead poisoning
- multiple mononeuropathy such as vasculitis, diabetes mellitus, leprosy, sarcoid, cryoglobulinemia

Neuropathy syndromes

- Predominantly autonomic disturbances
- Diabetes mellitus, amyloidosis, Guillan-Barré, porphyria, vincristine, botulism, paraneoplastic syndrome
- Predominantly painful
- Diabetes mellitus, amyloidosis, Guillan-Barré, uremia, arsenic poisoning
- Stocking and glove pattern polyneuropathy
- Circulating toxic factors.

Neuropathy syndromes

- Predominantly sensory disturbances
- Diabetes mellitus, alcohol, vitamin B_{12} deficiency, folic acid deficiency, excessive vitamin B_6 intake, vinca alakaloids, taxanes, cisplatin, amyloidosis, tabes dorsalis, monoclonal gammopathy, Friedrich's ataxia
- Asymmetrical proprioceptive loss (without paralysis)
- Paraneoplastic, excessive vitamin B_6 intake, cisplatin, Sjögren's

Charcot-Marie-Tooth (HMSN IA)

- Hereditary motor and sensory neuropathy
- One of the most common inherited neurologic disorders
- Autosomal dominant
- Presents in early adolescence or adulthood
- Foot drop and high stepped gait
- Loss of fine motor skills (first, in toes)
- “Inverted champagne bottle” appearance to lower legs as muscle bulk lost
- Duplication of PMP22 gene at 17p11.2 (peripheral myelin protein)
- Regulate Schwann cell growth and maturation

HMSN IB

- Myelin protein zero (MPZ) gene at 1p36.22 produces an identical clinical phenotype
- Adhesion molecule for myelin
- Another mutation involves the mitofusion protein 2, MFN2, at 1p36.22
- Prevents the mitochondrion from moving down the axon
- Synapse inoperative.

HMSN II

- Autosomal dominant.
- Clinical presentation is as with classic Charcot-Marie-Tooth.
- Loss of myelinated axons is prominent.
- Internodal demyelination is infrequent.
- Nerve conduction velocity impaired.
- Some cases involve mutations in the KIF1B gene at 1p36.22, encoding the microtubular transport motor, kinesin, that transports synaptic vesicles (neurons) and mitochondria (other cells)

HMSN II

- Others involve the MFN2 (mitofusion 2 protein) gene at 1p36.22 and affect mitochondrial structure.
- GARS1 gene (glycyl tRNA synthetase) at 7p14.3
- Associated with disease in hands.

HMSN III, now HMSN IVF

- Dejerine-Sottas disease
- Autosomal recessive
- Presents in early childhood
- Involves both trunk and limb muscles
- Mutations in genes encoding structural protein (connexin-32), protein degradation pathways (LITAF), and myelination induction (early growth response or EGR2).
- .

HMSN X

- X-linked dominant form
- GJB1 gene at Xq13.1 (gap junction or connexin-32 protein)
- Delayed transmission by radial diffusion
- Demyelination

Familial amyloid polyneuropathy

- Sensory neuropathy
- Loss of temperature sensation in the feet
- Orthostatic hypotension
- Incontinence.
- Autosomal dominant.
- TTR (Transthyretin) gene at 18q11.2-q12.1
- Amyloid deposits in vessel walls and endoneurium with axonal degeneration.

Refsum disease

- Mixed motor and sensory neuropathy
- Autosomal recessive
- Onset before 20 years of age.
- Night blindness and retinitis pigmentosa
- Loss of smell
- Ataxia as later development
- Icthyosis as later development
- PEX7 gene at 6q23.3 with PHYH gene at 10p13
- Perioxisomal enzyme phaytanoyl CoA deficiency.
- Phytanic acid accumulates

Metachromatic leukodystrophy

- Most common
- Occurs in infancy
- Autosomal recessive.
- ARSA gene at 22q13.33 (Arylsulfatase A deficiency from sulfatide).
- PSAP gene at 10q22.1 in a small number of cases (saposin B protein that works with arylsulfatase A)
- Myelin loss

Metachromatic leukodystrophy

- Initial presentation:
- Muscular weakness and wasting
- Stumbling gait
- Knock knees
- As the disease progresses:
- Spastic quadriparesis
- Cortical blindness and deafness
- Adult form presents with dementia

Krabbe disease

- Presents at 6 months of age
- Psychomotor retardation
- Hypertonia and opisthotonus
- Tonic seizures, spasticity, blindness
- Blindness and deafness.
- Autosomal recessive.
- GALC gene at 14q31.3 (β-galactosylceramidase deficiency)
- Cannot break down galactosylceramide or psychosine formed in myelin production
- Psychosine is toxic

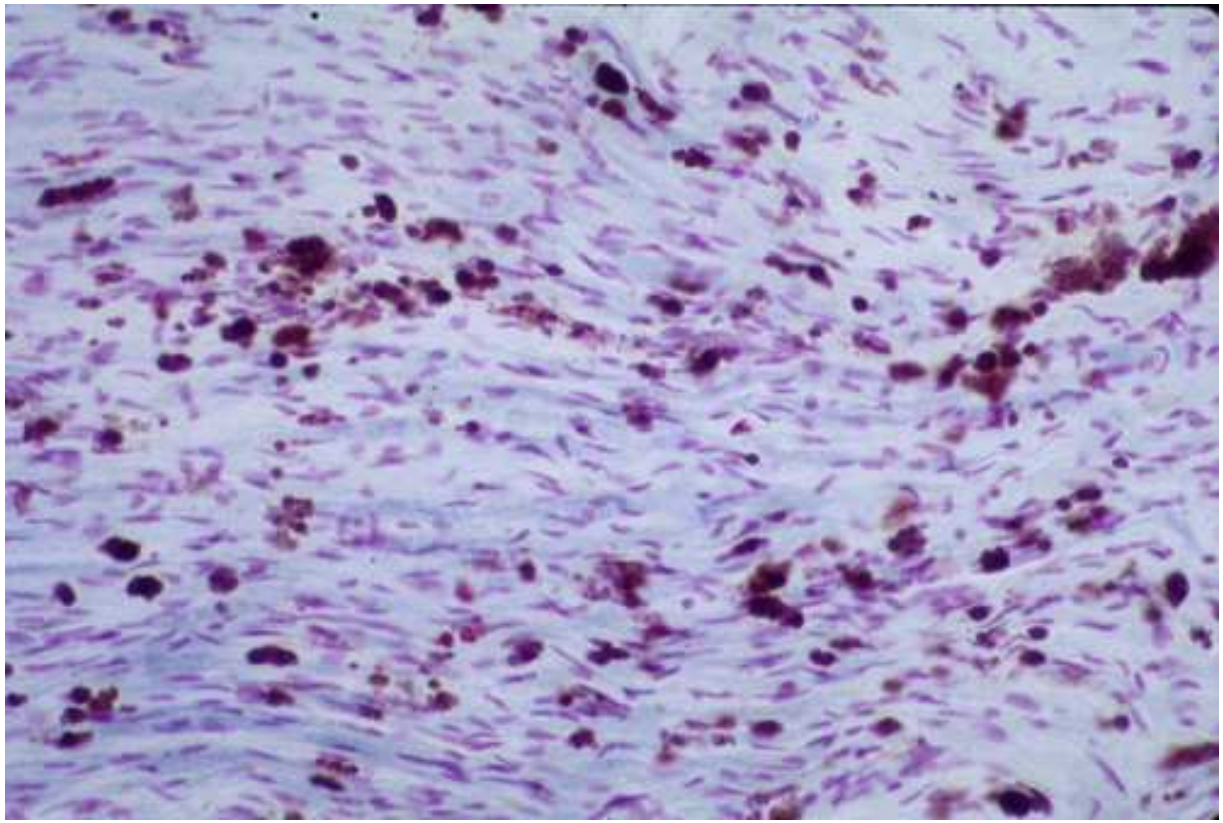
Krabbe disease

- Characterized histologically by nearly complete loss of oligodendroglia and myelin
- Epithelioid globoid cells found about blood vessels.in white matter
- Absence of myelin with sparing of arcuate fibers

Leukodsytrophy

- Krabbe disease.
- Autosomal recessive disorder
- Deficiency of galactocerebroside-β-galactosidase.

Leukodystrophy



Myelin loss.
Few oligodendroglial cells.
Lipid laden macrophages.

http://neuropathology-web.org/chapter10/images10/10-mldl.jpg
Accessed 11/26/2019

Leukodystrophy

- Adrenal leukodystrophy.
- X-linked
- Cerebral form
- Presents between 4-10 years
- Learning and behavioral disability
- Adrenal insufficiency

Leukodystrophy

- Adrenomyeloneuropathy form
- Presents between early adulthood and middle age
- 4% of females are symptomatic
- Paraparesis
- Bladder and bowel dysfunction
- Adrenal insufficiency

Leukodystrophy

- Addison disease only
- Presents any time between childhood and adulthood
- Adrenal insufficiency
- Paraparesis, bladder and bowel dysfunction appear later
- ALDP gene at X28
- Elevated levels of long chain fatty acids in serum and tissues as a result of deficiency in enzyme that degrades very long chain fatty acids.
- More severe demyelination noted in cortex (particularly, parietal-occipital region)

Leukodystrophy

- Alexander disease.
- Neonatal form
- First month of life
- Hydrocephalus
- Seizures
- Infantile form
- Presents before age 2
- Megalencephaly
- Seizures
- Stiffness and spasticity in limbs
- Intellectual disability and developmental delay

Leukodystrophy

- Juvenile form
- Occurs from childhood to adulthood
- Speech and swallowing difficulties
- Ataxia
- Autosomal dominant
- GFAP gene at 17q21.31
- Rosenthal fibers (glial fibrillary acidic proteins in glial cells and around blood vessels)
- Demyelination.

Molecular change

- ABCD1 gene at Xq28 (ATP Binding Cassette Transporter)
- Adrenaleukodystrophy protein production impaired
- Elevated levels of long chain fatty acids in serum and tissues as a result of deficiency in enzyme that degrades very long chain fatty acids.
- Segmental demyelination with onion bulbs as well as myelinated and unmyelinated axonal degeneration noted.
- More severe in parietal and occipital regions
- Linear inclusions are present in Schwann cells.

HSAN I

- Hereditary sensory and autonomic neuropathy
- Loss of pain and temperature sensation early
- Lancinating pain
- Orthostatic hypotension
- Without muscle weakness.
- Autosomal dominant
- Presents in young adults
- SPTLC1 gene at 9q22.31
- Cys133Trp common mutation
- Serine palmitoyl transferase, long chain base unit.
- Produces deoxysphingoid bases (abnormal), diminishing production of sphingolipid

- HSAN IB
- Sensory neuropathy with cough
- GERD
- 3p22-24
- HSAN IC
- Presents as HSAN IA
- SPTLC2 missense mutation

- HSAN ID
- Distal sensory loss and amyotrophy of lower limbs
- ALT1 gene encodes atlastin-1
- Reduced GTPase activity
- Also associated with hereditary spastic paraplegia
- HSAN IE
- Somatosensory loss
- Sensorineural hearing loss
- Dementia
- DNMT1 gene at (DNA methyltransferase)

Inherited neuropathies

- HSAN II
- Presents in childhood
- Sensory neuropathy
- GERD
- Autosomal recessive
- WNK/HSAN2 gene at 12q13.3. (HSAN IIA)
- Regulate Na^+ and K^+ channel transport
- RETREG1 gene at 5p15.1 (HSAN IIB)
- Autophagy
- Axonal degeneration of myelinated fibers prominent in HSAN I and HSAN II.

Inherited neuropathies

- HSAN III (Riley-Day syndrome).
- Presents in infancy
- Autonomic neuropathy
- Autosomal recessive
- ELP1 (IKPKAP) gene at 9q31.3 (histone acetyltransferase)
- Affects transcription of proteins that deal with cytoskeleton and with cell motility
- Described in Ashkenazi cohorts.
- Axonal degeneration of unmyelinated fibers with atrophy and loss of sensory and autonomic ganglion cells

Inherited neuropathies

- HSAN IV
- Presents in infancy
- Congenital insensitivity to pain
- Anhidrosis
- Autosomal recessive
- NTRK1 gene at 1q23.1-22
- Neurotrophic tyrosine kinase receptor type I affects phosphorylation
- Nearly complete loss of small unmyelinated and myelinated fibers prominent

Inherited neuropathies

- HSAN V
- Presents in infancy
- Insensitivity to pain and temperature
- Nearly complete loss of small myelinated fibers
- autosomal recessive
- NGFB gene at 1p31.1
- Nerve growth factor β-subunit affects phosphorylation
- HSAN V shows loss of myelinated fibers

Hereditary spastic paraplegia

- Pure form (Troyer syndrome)
- Presents in second and fourth decades
- Progressive upper motor neuron disease with spasticity in legs and urinary urgency
- Gait disturbance
- Impaired pain sensation
- 75-80% of affected individuals
- Autosomal dominant
- SPART gene at 13q13.3
- Spartin regulates endocytosis (here, nonfunctional)

Hereditary spastic paraplegia

- Complex form
- Ataxia in 30%
- Seizures
- Cognitive impairment
- Possible upper limb involvement

Hereditary spastic paraplegia

- Autosomal dominant
- HSP IIIA
- Presents at age 4
- 15% of cases
- Lower limb disease with hyperactive bladder
- ATL-1 gene at 14q21.3
- Atlastin
- HSP IV
- Also describes hyperreflexia
- SPAST gene at 2p23
- Spastin regulates microtubule transport
- 40% of cases

Hereditary spastic paraplegia

- Autosomal dominant
- HSP Type 31
- Ages 20-30
- Spasticity and amyotrophy
- REEP1 gene at 2p11.2
- Impaired activation of G-coupled receptors
- Function in mitochondria unknown
- 5% of cases

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 5A
- Presents from infancy to adulthood
- CYP7B1 gene at 8q12.3 (P450 system)
- Oxysterol-7-α-hydroxylase
- Impaired hydroxylation of nuclear DHEA leads to cholesterol accumulation
- 7% of cases

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 7
- Adult onset
- Pure: spastic paraplegia
- Complex: with cerebellar dysfunction
- 5% of cases
- CYP7B1 gene at 8q12.3 (P450 system)
- Oxysterol-7-α-hydroxylase
- Impaired hydroxylation of nuclear DHEA leads to cholesterol accumulation

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 11
- SPG11 gene at 15q21.1
- Thin or absent corpus callosum (radiographic evidence) prominent finding
- Spatacsin involved in axon maintenance
- 5% of cases
- X-linked recessive
- Cognitive impairment common
- L1CAM gene at Xq28
- Adhesion molecule