

Degenerative CNS Diseases

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DEGENERATIVE CNS DISEASES - function deterioration over extended period of time.

- most are **genetic** with *metabolic basis*.
- may start with difficult to recognize *losses in motor, cognitive, language skills*.
- another possible onset – *seizures*.
- screening studies:
 - blood** – glycemia, ammonium, lactate, pyruvate, pH, lysosomal enzymes.
 - urine** – amino acids (for aminoacidopathies), organic acids (for fatty acid metabolism disorders), bile acids (for peroxisomal disorders).
 - skin fibroblasts** – microscopic abnormalities, missing enzymes.

LEUKODYSTROPHIES

- diseases of **white matter** - *progressive loss of myelin*. see p. Dem11 >>
UMN signs are prominent early!

NEURODEGENERATIVE DISEASES

- diseases of **gray matter** - *progressive loss of neurons* with associated secondary **white matter** changes.
- neuronal loss is *selective* - *affects one related groups of neurons, while others leaving intact* – “SYSTEM DEGENERATIONS”.

ETIOLOGY

- unknown (some diseases are inherited) – diseases arise *without any clear inciting event* in patients *without previous neurologic deficits*.

CLINICAL HALLMARK

- *progressive deterioration of neurologic function* (with loss of speech, vision, hearing, locomotion, often associated with seizures, feeding difficulties, intellect impairment).
 Most common clinical manifestations – **seizures & dementia!**

NEUROPATHOLOGIC FINDINGS

- differ greatly:
 - a) specific **intracellular** abnormalities (e.g. Lewy bodies, neurofibrillary tangles).
 - b) only loss of affected **neurons** (accompanied by neuronophagia and reactive fibrillary **gliosis**).

CLASSIFIED

- according to **CNS anatomic regions** that are **PRIMARYLY** affected:
 - a) cerebral cortex (e.g. Alzheimer disease)
 - b) subcortical areas (e.g. Huntington disease, Parkinson disease, Wilson disease)
 - c) cerebellum (e.g. spinocerebellar ataxias)
 - d) diffuse (e.g. Tay-Sachs disease, Gaucher disease, Niemann-Pick disease)
 - e) dorsal root ganglia (e.g. Fabry disease)

DIAGNOSIS

- until recently, routine **brain and rectal biopsies** were performed; with advent of modern **neuroimaging** and **biochemical** diagnostic tests, these invasive procedures are now rarely necessary.

TRINUCLEOTIDE REPEAT DISEASES (TRD)

- genetic diseases affecting nervous system characterized by **trinucleotide repeat** expansion (i.e. *expansion of normal genome by runs of three DNA bases*).
- can be inherited as *autosomal dominant* (most commonly), autosomal recessive, or X-linked disorders.
- mechanism for trinucleotide expansion is not well understood.
- most involve CAG repeats; others involve CGG repeats, CTG repeats - all these are in exons (GAA repeat in intron causes Friedreich's ataxia).
- repeat involves:
 - a) **coding region (exon)** → *adult-onset, gain-of-function* disorders.
 - b) **noncoding region (intron)** → *early-onset, loss of function* disorders involving multiple organs.
 - c) genetic sequence **outside of gene** in 5' or 3' untranslated region (e.g. fragile X gene, myotonic dystrophy gene).

Disease	Chromosome - Gene	Triplet Repeat	Normal Size Repeat	Expanded Repeat Size
Fragile X syndrome	FMR-1	CGG	2-50	> 200
Huntington disease	4p16.3 - huntingtin	CAG	11-34	37-121
Friedreich's ataxia	9q13 - frataxin	GAA	7-22	200-900
Myotonic dystrophy (s. Steinert disease)	19q13.2-3 - DM protein kinase	CTG	5-30	50-thousands
Spinocerebellar ataxia 1	6p21.3 - ataxin-1	CAG	6-39	40-81
Spinocerebellar ataxia 2	12q23-24 - ataxin-2	CAG	15-29	35-59
Spinocerebellar ataxia 3 (Machado-Joseph disease)	14q24.3-qter - ataxin-3	CAG	12-40	67-200

Disease	Chromosome - Gene	Triplet Repeat	Normal Size Repeat	Expanded Repeat Size
Spinocerebellar ataxia 6	19p13.1 - α_{1A} voltage-dependent Ca^{2+} channel	CAG	4-16	21-27
Spinocerebellar ataxia 7	3p14-21.1 - ataxin-7	CAG		
Dentatorubral-pallidoluyasian atrophy	12p12.3-13.1 - atrophin	CAG	7-23	49-79
BSMA (bulbospinal muscular atrophy)	Xq11-12 - androgen receptor	CAG	11-33	40-66

- all TRD primarily involve neurologic phenotypes.
- *number of repeats* correlates with *disease severity*.
- repeats are **unstable in gametes** - change in number of repeats is transmitted to next generation, sometimes with decrease in number, but more often with increase (→ earlier disease onset and more severe phenotype in offspring – ANTICIPATION).
 - there is frequently predilection for expansion during meiosis in *parents of one sex* - mother (e.g. fragile X syndrome, myotonic dystrophy) or father (e.g. Huntington disease, spinocerebellar ataxia type I).
- some disorders have intermediate stage (PREMUTATION) - expansion beyond normal range, but not enough to cause disorder

BIBLIOGRAPHY for ch. “Metabolic Disorders” → follow this [LINK >>](#)