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 >>](http://www.neurosurgeryresident.net/Dem.%20Demyelinating%20disorders\Dem11.%20Leukodystrophies.pdf)

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:

1. specific **intracellular** abnormalities (e.g. Lewy bodies, neurofibrillary tangles).
2. only loss of affected **neurons** (accompanied by neuronophagia and reactive fibrillary **gliosis**).

Classified

- according to CNS anatomic regions that are primarily affected:

1. cerebral cortex (e.g. Alzheimer disease)
2. subcortical areas (e.g. Huntington disease, Parkinson disease, Wilson disease)
3. cerebellum (e.g. spinocerebellar ataxias)
4. diffuse (e.g. Tay-Sachs disease, Gaucher disease, Niemann-Pick disease)
5. 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:

1. **coding region (exon)** → adult-onset, gain-of-function disorders.
2. **noncoding region (intron)** → early-onset, loss of function disorders involving multiple organs.
3. 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 |
| **Spinocerebellar ataxia 6** | 19p13.1 - **α1A voltage-dependent Ca2+ channel** | CAG | 4-16 | 21-27 |
| **Spinocerebellar ataxia 7** | 3p14-21.1 - **ataxin-7** | CAG |  |  |
| Dentatorubral-pallidoluysian 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 >>](http://www.neurosurgeryresident.net/Mus.%20Muscular,%20Neuromuscular%20disorders\Mus.%20Bibliography.pdf)

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