Degenerative CNS Diseases

Last updated: April 19, 2019

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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 – glycerina, ammonium, lactate, pyruvate, pH, lysosomal enzymes.
- urine – amino acids (for aminosudopathies), organic acids (for fatty acid metabolism disorders), bile acids (for pelliosis disorders)
- skin fibroblasts – microscopic abnormalities, missing enzymes.

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

LEUKODYSTROPHIES

- diseases of white matter – progressive loss of myelin

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”.

REFRACTORY

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

CLINICAL-PATHOLOGIC

- 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 neuronalphagia and reactive fibrillary gliosis).

CLASSIFIED

- according to CNS anatomic regions that are PRIMARILY 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)

DIAGNOSTIC

- 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 DESEASES (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).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome - Gene</th>
<th>Triplet Repeat</th>
<th>Normal Size Repeat</th>
<th>Expanded Repeat Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome</td>
<td>FMR-1</td>
<td>CAG</td>
<td>2-50</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>4p16.3 - huntingtin</td>
<td>CAG</td>
<td>11-34</td>
<td>17-121</td>
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<tr>
<td>Friedreich's ataxia</td>
<td>9q13.3 - frataxin</td>
<td>GAA</td>
<td>7.2-72.0</td>
<td>200-900</td>
</tr>
<tr>
<td>Myotonic dystrophy (s. Steinert disease)</td>
<td>19q13.2-3 - DM protein kinase</td>
<td>CTT</td>
<td>5-30</td>
<td>50-thousands</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 1</td>
<td>6p21.3 - ataxin-1</td>
<td>CAG</td>
<td>6-39</td>
<td>40-81</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 2</td>
<td>12q32.24 - ataxin-2</td>
<td>CAG</td>
<td>15-29</td>
<td>35-59</td>
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<tr>
<td>Spinocerebellar ataxia 3</td>
<td>14q24.3-qter - ataxin-3</td>
<td>CAG</td>
<td>12-40</td>
<td>67-200</td>
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<tbody>
<tr>
<td>Spinocerebellar ataxia 6</td>
<td>19p13.1 - α1A voltage-dependent Ca2+ channel</td>
<td>CAG</td>
<td>4-16</td>
<td>21-27</td>
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<tr>
<td>Spinocerebellar ataxia 7</td>
<td>3p14.21.1 - ataxin-7</td>
<td>CAG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentatonubral-pallidoluysian atrophy</td>
<td>12p12.3-13.1 - atrophin</td>
<td>CAG</td>
<td>7-23</td>
<td>49-79</td>
</tr>
<tr>
<td>BSMA (bulbospinal muscular atrophy)</td>
<td>Xq11-12 - androgen receptor</td>
<td>CAG</td>
<td>11-33</td>
<td>40-66</td>
</tr>
</tbody>
</table>

- 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 1).
- some disorders have intermediate stage (PREMUTATION) - expansion beyond normal range, but not enough to cause disorder.

BIBLIOGRAPHY for ch. “Metabolic Disorders” → follow this LINK >>