CNS lecture 6

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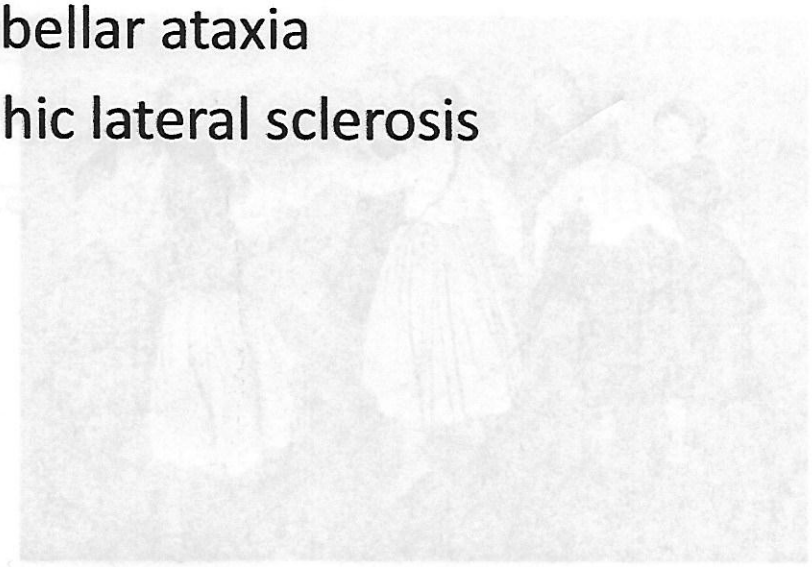
Neurodegenerative disorders 2

④ • Huntington disease
⑤ • Spinocerebellar ataxia
⑥ • Amyotrophic lateral sclerosis



4 Huntington disease

- Autosomal dominant ⇒ inherited disease
- Movement disorder which is chorieform =dancelike Begins with problems in movements
- Degeneration of caudate and putamen

* Affects males more

Choreiform movement

- Chorei = Greek word = circle dance

Chorieform movement

- Involuntary jerky movements of all parts of the body .

Clinical course

- Progressive (first movement → then cognitive)
- Memory loss can develop and progresses to severe dementia

occurs later ←

- Behavioural changes.. Risk of suicide

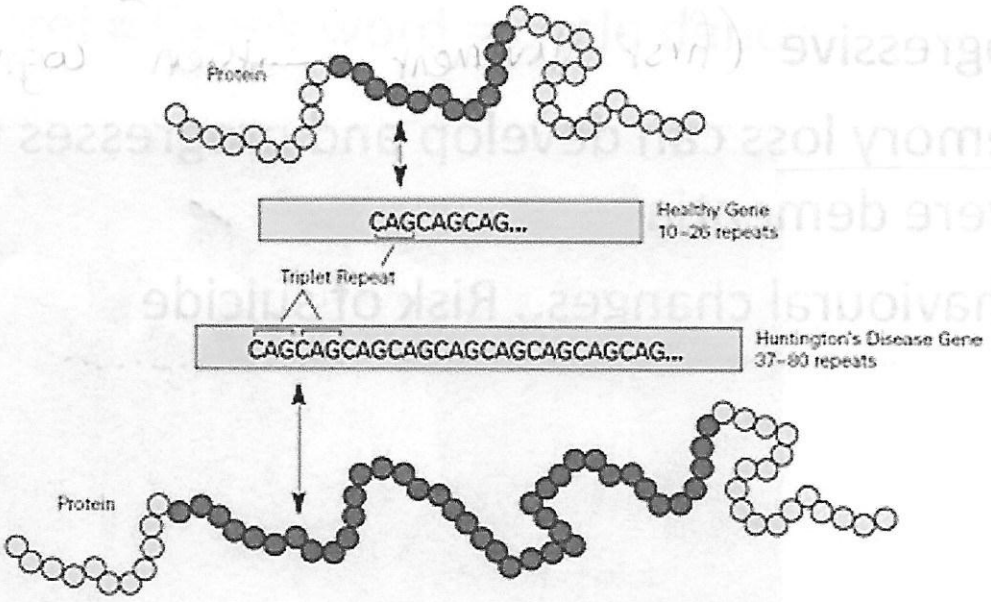
pathogenesis

- CAG(cytosine-adenine-guanine) trinucleotide repeat expansions in the gene that encodes huntingtin protein.
- CAG codes for glutamine ⇒ ↑glutamine

- Huntingtin protein is thought to play a role in long term memory storage

Normally ⇒ CAG is repeated up to 35 copies

Huntington ⇒ CAG trinucleotide is repeated lots of times (around 100 times)



- Normally CAG repeated between 11-35 times
- Huntington disease, repeats more than 35
- The more number of the repeats, the earlier the onset of symptoms
- Course of disease not affected by number of repeats

↑ repeats → course is same (same severity)
BUT onset is earlier

- The abnormal huntingtin protein.. Contains polyglutamine tract
- it forms large intra-nuclear aggregates
- These aggregates cause functional problems leading to the symptoms of Huntington disease

morphology

- Small brain
- Atrophy of caudate and putamen
- Severe loss of neurones

5 Spinocerebellar ataxia

- Ataxia; Greek = lack of order

Spinocerebellar ataxias

Problem in spinal cord + cerebellum

- Heterogeneous group of diseases
- Trinucleotide repeat expansion mutations.
- Group of diseases that differ in the mutation type, inheritance pattern, age of onset and clinical symptoms.
- Affects cerebellar cortex, spinal cord, other brain regions and peripheral nerves

↗ Some related to glutamine + some to other proteins

- Affected areas: neuronal degeneration and gliosis
- Some types associated with CAG trinucleotide repeat expansion. (Glutamine)

Other types → other trinucleotides

Friedreich ataxia

- Autosomal recessive
- Manifests in the first decade of life (early)
- Gait ataxia and hand clumsiness and dysarthria
- High incidence of cardiac disease and DM
- Due to GAA repeat expansion.. Coding for frataxin; a protein that regulats cellular iron level

Friedreich ataxia

- Frataxin... important in iron levels especially in the mitochondria
- The repeat mutation causes transcription silencing.. Decreased frataxin.. Causes mitochondrial dysfunction and increased oxidative damage

6 Amyotrophic lateral sclerosis (ALS)

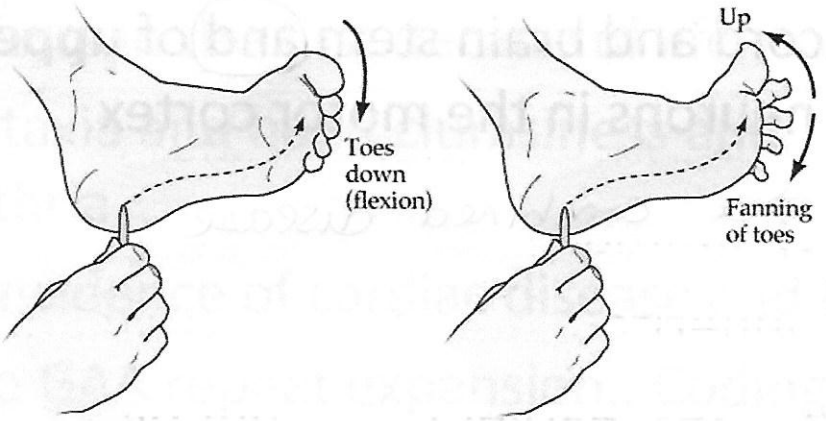
- Due to death of **lower** motor neurons in the spinal cord and brain stem and of **upper** motor neurons in the motor cortex.

⇒a combined disease

ALS

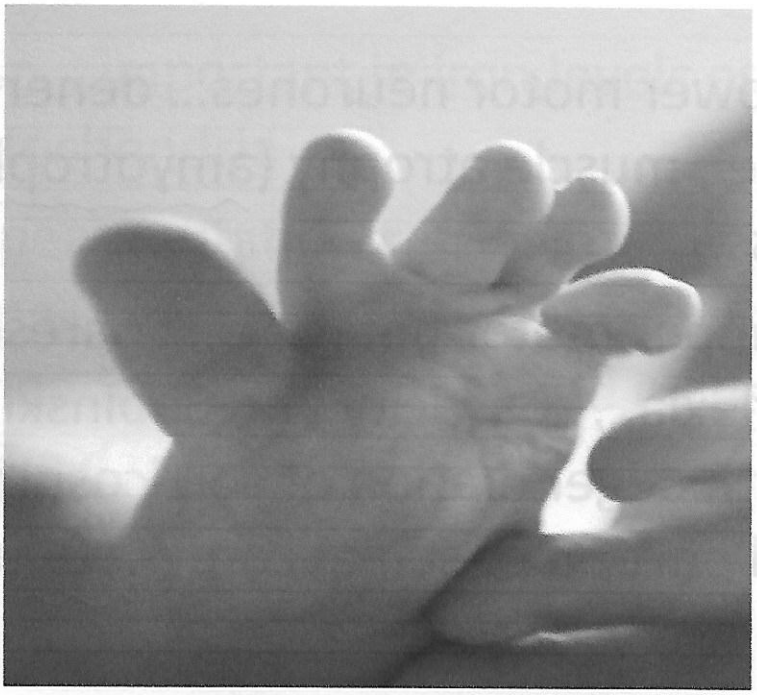
- Loss of lower motor neurones… denervation of muscle , muscle atrophy (amyotrophic)and weakness.
- Loss of upper motor neurones… paresis, hyperreflexia, , spasticity and Babinski sign, along with degeneration of corticospinal tracts in lateral portion of spinal cord (lateral sclerosis)

Babinski sign



Normal plantar response

Extensor plantar response
(Babinski sign)



ALS

- Sensation NOT affected.
- Cognitive impairment occurs.
- Males slightly more than females
- Majority sporadic
- 5-10% inherited; autosomal dominant
- familial cases: earlier onset but disease progression similar

How to remember neurodegenerative disorders?

- Make a table and compare!!!