Huntington’s Disease

* inherited neurodegenerative disorder
  – autosomal dominant
  – 100% penetrance
* age of onset: 35 - 45 yr
* juvenile variant
  – 5-10% of affected individuals

Huntington’s Disease

* motor, cognitive, and behavioural dysfunction
* inexorably progressive
  – death 15 - 20 yr after symptom onset
Huntington’s Disease
• prevalence
  – 10 / 100,000 population
• Movement Disorders Clinic
  – about 65 symptomatic patients

Chorea
• irregular, unpredictable, purposeless, rapid movements that flow randomly from one body part to another
• Huntington’s disease

Huntington’s Disease
Clinical Features - 1
• motor dysfunction
  – chorea is usually the earliest sign
    • initially fingers, toes, face
    • progressive
  – motor impersistence
  – eye movement abnormalities
    • impaired initiation of saccades
    • slow saccades
Huntington’s Disease
Clinical Features - 2
• motor dysfunction
  – dystonia and parkinsonism
  – progressive incoordination, unsteadiness, immobility, dysarthria, dysphagia
  – motor signs eventually appear in all

Huntington’s Disease
Clinical Features - 3
• juvenile onset
  – rigidity, dystonia, bradykinesia, myoclonus
  – seizures
  – rapidly progressive dementia

Huntington’s Disease
Clinical Features - 4
• cognitive impairment
  – executive function is thought to be selectively lost
  – cortical deficits absent (aphasia, agnosia, apraxia)
Huntington's Disease
Clinical Features - 5

- cognitive impairment
  - some degree of impairment is inevitable
  - occasionally minimal
  - rate of progression varies considerably

Huntington's Disease
Clinical Features - 6

- behavioural changes
  - gradual change in personality
  - affective disorders in 30-40%
  - schizophrenia and other psychoses in 10%
  - alcohol abuse; high suicide risk

Huntington's Disease
Neurobiology - 1

- pathology
  - striatal atrophy
  - neuronal loss and gliosis
    - most striking in, but not limited to striatum
    - diffuse cortical changes, primarily frontal
  - degree of pathology is related to the duration of symptomatic HD
Huntington’s Disease
Neurobiology - 2

Huntington’s Disease
Neurobiology - 3

*selective neuronal loss
– striatal projection neurons are affected
  • medium spiny neurons (GABA)
– striatal interneurons are spared
  • SS/NPY
  • cholinergic

Figure 4 Results of the voxel based morphometric analysis of the Huntington’s disease patient subgroups vs age matched controls: panels A and B for the criterion motor deficits; panels C and D for the criterion cognitive deficits. All regions are shown where the corresponding subgroup (n = 12 each) had a significantly decreased grey matter density in comparison with an age matched group of normal controls (n = 15 each) at p
Figure 1. Caudate volume and estimated years to onset (YTO) in preclinical subjects

Aylward EH et al. Neurology 2004;63:66-72

Figure 2. Longitudinal change in caudate volume for preclinical subjects

Aylward EH et al. Neurology 2004;63:66-72

Huntington's Disease
Genetics - 1
- autosomal dominant
- chromosome 4
- very low spontaneous mutation rate

Huntington's Disease
Genetics - 2


Human IT15 Gene

Normal

(CAG) 5 - 35

Huntington's Disease

(CAG) 40 - 240
Huntington’s Disease
CAG Repeat Number - 1

< 27 normal
27-35 ‘mutable normal’
36-39 ‘reduced penetrance’
> 39 HD phenotype


Huntington’s Disease
CAG Repeat Number - 2


Huntington’s Disease
CAG Repeat Number - 3

Nature Genetics Reviews
Huntington’s Disease

Diagnosis

• CAG repeat analysis
  ➢ determine the presence of the gene

• diagnosis of symptomatic HD is based on the clinical features

• supportive counselling is crucial before, during, and after DNA testing, regardless of whether or not the patient is symptomatic

IT15

• universal expression in multiple tissues
• new class of protein important to neuronal function
  – huntingtin
  – 3144 amino acids, m.w. = 348 kDa
• no evidence of regional selectivity in brain
  – neurons and glia
**Huntingtin**

- Transgenic mouse models
  - Significantly reduced levels associated with aberrant brain development and perinatal lethality
  - Normal levels, even of mutant huntingtin, is associated with normal brain development
- Critical role in neurogenesis

**Huntington’s Disease**

**Cellular Mechanisms**

- **Huntingtin** - Normally localized in cytoplasm
- **In HD** - Neuronal intranuclear inclusions
  - Huntingtin and ubiquitin
  - Associated nuclear membrane changes
  - Precedes phenotypic changes (transgenic mice)

**Huntington’s Disease**

**Cellular Mechanisms**

- Translocation of mutant huntingtin from cytoplasm to nucleus may represent the dominant gain of function
Huntington’s Disease
Pathophysiology

• animal models
  – intrastriatal kainic acid
    • McGeer EG, McGeer PL. Nature 1976;263:517-519
    • Coyle JT, Schwarcz R. Nature 1976;263:244-246
  – intrastriatal quinolinic acid
    • Beal F and others

Huntington’s Disease
Pathophysiology

• excitotoxic hypothesis
  – intrastriatal injection of excitotoxic amino acids mimics the characteristic pathology of HD
  – toxicity can be prevented by NMDA antagonists
  – but acute striatal lesion is unlike the slow insidious cell loss associated with neurodegenerative disease

Huntington’s Disease
Weak Excitotoxic Hypothesis

Impaired mitochondrial energy metabolism

\[ \downarrow \]

Neuronal sensitivity to endogenous glutamate

\[ \uparrow \]

Gradual loss of neurons

(final mechanism = excitotoxicity)
**Weak Excitotoxic Hypothesis**

- 3-NPA
  - inhibits succinate dehydrogenase and complex II
  - associated with striatal pathology similar to HD
  - blocked by NMDA antagonists

**Huntington’s Disease**

*Current Treatment*

- symptomatic

*Experimental Treatment*

- goal
  - to delay or prevent the onset of symptomatic HD in the asymptomatic individual
Huntington's Disease
Experimental Treatment

- postulated mechanisms
  - excitotoxicity
  - impaired mitochondrial metabolism

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[Diagram of cortico-striatal neuron showing glutamate release, calcium ions (Ca\(^{2+}\)), NMDA, GLY, and PCP pathways with lamotrigine and riluzole labels]
Electron Transport Chain

Succinate

Complex I

NADH

Ubiquinone

Cytochrome C

Coenzyme Q10

Complex III

Complex IV

O2

CARE - HD
(αCo-enzyme Q10 and Remacemide in HD)

• multi-centre, placebo-controlled, randomized, prospective trial
• 2 x 2 factorial design
• 347 patients with symptomatic HD
• 30 month follow-up, using validated clinical rating scales (UHDRS)
• Huntington Study Group; NIH funded
CARE - HD
(Co-enzyme Q₁₀ and Remacemide in HD)
• end-point = total functional capacity


Huntington’s Disease
Experimental Treatment
• 2CARE
  – Co Q₁₀ 2400 mg/d
Huntington’s Disease
Experimental Treatment

- minocycline
  - caspase I inhibition