Neurodegenerative Diseases: Huntington’s disease
Huntington’s Disease: Outline

1. Symptoms
2. Neuropathology and how it contributes to symptoms
3. Huntingtin gene
4. What initiates neurodegeneration?
• New York, 1872
• Hereditary
• Chorea (Greek: to dance): Hyperkinetic involuntary movements, slowing of voluntary movements
• 1983: HD caused by single gene
• 1993: Huntingtin gene
• Inherited autosomal dominant
• Huntington gene mapped to chromosome 4 after study of high incidence population near Lake Maracaibo, Venezuela
• Salem Witch Trials, 1692

Woody Guthrie
### 1. Clinical Features of HD

<table>
<thead>
<tr>
<th>Motor Dysfunction</th>
<th>Cognitive Dysfunction</th>
<th>Psychiatric Problems</th>
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<tbody>
<tr>
<td>• Chorea</td>
<td>• Dementia</td>
<td>• Subtle personality change, apathy, irritability, disinhibition</td>
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<td>• Gait abnormalities</td>
<td>• Problem solving, planning, mental slowing, poor attention</td>
<td>• Mood swings</td>
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<td>• Inco-ordination</td>
<td>• Depression</td>
<td>• Social withdrawal</td>
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<td>• Dysarthria (slurred speech)</td>
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<td>• Suicide and self-harm</td>
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<td>• Eye movement abnormalities</td>
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<td>• Rigidity/bradykinesia/dystonia</td>
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2. Pathology of HD
Basal Ganglia and the motor system

- Serve to modulate activity of neurons of the motor regions of the cortex.

- Feedback circuits

- Not crucial for initiation of movement. Important for quality and correctness of movement
The Human Basal Ganglia

- Putamen
- Globus pallidus (lateral part)
- Globus pallidus (medial part)
- Amygdala
- Caudate nucleus
- Thalamus
- Subthalamic nucleus

- Motor cortex
- Thalamus
- Tectum
- Superior colliculus
- Inferior colliculus
- Red nucleus
- Reticular formation
- Pons
- Vestibular nucleus
- Medulla oblongata
- Cerebellar nuclei
Figure AB-18: Basal Ganglia

- Cortex
- Caudate Nucleus
- Putamen
- Thalamus
- Subthalamic Nucleus
- Globus Pallidus
- Substantia Nigra
- Hypothalamus
Basal Ganglia Circuitry

Cerebral Cortex

Stimulation of cortex increases movement

Striatum

D1
Sub P
GABA

D2
Enk
GABA

Glu

GPe
GABA

STN
GABA

Glu

VA/VL
Thal

GABA

SNpc

SNpr

DA

GABA

GABA

direct pathway

indirect pathway
Hyperkinetic movement

Early Huntington’s Disease

- **Cerebral Cortex**
  - Glu
  - Increased cortical output increases movement
  - Thal disinhibited

- **Striatum**
  - D1 (Sub P GABA)
  - D2 (Enk GABA)
  - GABA
  - GPe
  - STN
  - GABA
  - GABA
  - VA/VL Thal

- **Sub C'trum**
  - SNpc
  - SNpr
  - GABA
  - VA/VL Thal
  - GABA
  - GABA

- **DA**
  - GABA
Hypokinetic movement

**Late Huntington’s Disease**

striatal projection neurons degenerate

Striatum

- D1: Sub P GABA
- D2: Enk GABA

Cerebral Cortex

cortical neurons degenerate

DA

SNpc
SNpr

GPe

STN

GPe

GABA

GABA

GABA

Glu

Glu

VA/VL Thal

both direct and indirect pathways affected
3. What causes HD?
• In mouse model, accumulation of mutant huntingtin first observed in striatal medium spiny neurons

• WT huntingtin normally located in cytoplasm

• Mutant huntingtin:
  – accumulates in nucleus in inclusions
  – Induces apoptosis when transfected into cultured striatal neurons
Huntingtin Gene (HTT)

- >39 CAG repeats codes for protein with glutamine repeats = gain of function mutation

- Age of onset and severity of neuronal degeneration depends on length of repeat
Some ethical points

• Due to the late onset of disease, many would have already had children by the time they find out they have it

• Ethical debates raised by question of genetic testing
  – When should a person be tested?
  – Do parents have the right to choose for children?
  – Does an insurance company have the right to know the results of genetic tests?
Huntingtin protein
Huntingtinin protein

HTT with expanded polyglutamine at N terminus toxic to neurons
1. Forms neuropil aggregates – Dystrophic neurites
2. Neuronal intranuclear inclusions
4. What initiates neurodegeneration?

1. Neuronal mechanisms
   - Protein aggregation
   - Oxidative stress/mitochondrial damage and excitotoxicity
   - Apoptosis

2. Intercellular mechanisms
   - Astrocyte-mediated toxicity
   - Microglia-mediated toxicity
Key features of HD pathogenesis

- Expanded CAG (exon 1 htt gene)
- Mutant Huntingtin Protein
  - Transcriptional Dysregulation
  - Protein interactions & aggregation
- Cellular Dysfunction
  - Autophagy
  - Apoptosis
- Cell Death
  - Ubiquitin Proteasome Pathway
  - Mitochondrial Cell Death

Clinical Disease Phenotype
Aggregates

Abnormal HTT accumulates in intranuclear inclusion bodies

Davies, Cell, 1997
Aggregates

- Aggregates also arise in cytoplasm, dendrites, axon terminals
- Fibrillar appearance
- Density correlates with CAG repeat length
- Transfection of glioblastoma cell line with mutant huntingtin: aggregates.
- Death of cells showing nuclear fragmentation (hallmark of apoptosis)
Aggregates

- Blocking aggregation can inhibit toxicity
- But! Cells with inclusions have less likelihood of dying compared to cells with diffuse mutant HTT
- Density of visible aggregates does not correlate with distribution of cell death

- Aggregates vs aggregation
- Site of aggregate may matter: soma vs. blocking process
- Aggregates may still be more toxic than WT protein
- Therapeutic benefits of anti-aggregation?
Ross & Tabrizi, Lancet Neurology, 2011
Mitochondria

**COMPLEX I**
NADH-CoQ oxidoreductase

**COMPLEX II**
succinate dehydrogenase

**COMPLEX III**
cytochrome bc₁ complex

**COMPLEX IV**
cytochrome c oxidase

CITRIC ACID CYCLE

Intermembrane space

Outer membrane

Inner membrane

Cristae

NAD⁺

H⁺

NADH

succinate

fumarate

H⁺

e⁻

Q

Cyt C

O₂

2H₂O

4H⁺
Mitochondrial dysfunction and oxidative stress
Mitochondrial dysfunction and HD

• Injection of mitochondrial complex II inhibitors (malonate and 3-nitropropionic acid) in rats
  – Same pattern of striatal pathology and choreiform movements as seen in patients

• Postmortem studies of HD patient brains:
  – Decreases in complexes II, III, IV in caudate and putamen
  – Increase in 8-hydroxydeoxyguanosine (measure of oxidative damage) in caudate
Reactive oxygen species and HD

- Cell model + mutHTT: Elevated levels of ROS
- ROS-modified DNA and proteins in HD mice and patients
- Increased SOD expression in HD cell model
- Rescue of cell death induced by mutHTT:
  - Express anti-oxidants, reduced glutathione or N-acetyl cysteine:
- Abnormalities of intracellular calcium ([Ca2?]i) handling is a well documented feature of huntingtin-mediated cellular dysregulation
Glutamate excitotoxicity

http://wwwchem.csustan.edu/chem4400/SJBR/Olson01.htm
HD mouse model +
- Coenzyme Q10 = mitochondrial cofactor
- Ramacemide = NMDA antagonist
- Extended survival, delayed development of motor deficits, weight loss, cerebral atrophy, NII in mouse model of HD

Ferrante, Journal of Neuroscience, 2002
Intercellular-mediated Neurodegeneration

1. Astrocytes

2. Microglia
HTT accumulates in astrocytes from HD mouse model

Shin, Journal of Cell Biology, 2005

130-repeat-HTT accumulates in astrocyte nuclei in culture

Shin, Journal of Cell Biology, 2005
Expression of mutant HTT in astrocytes triggered the death of neurons not expressing mutant HTT

Transgenic expression of mutant HTT in astrocytes in mice causes a Huntington’s disease-like phenotype on its own, or exacerbates the neuronal phenotype in a HD model

Shin, Journal of Cell Biology, 2005
Microglia in HD

Tai, Brain, 2007: Microglial activation in presymptomatic HD gene carriers
Neuroinflammatory mediators in HD

Bjorkqvist, Journal of Experimental Medicine, 2008
Ross & Tabrizi, The Lancet Neurology, 2011
• Neuronal toxicity of HTT protein

• Intercellular mechanisms of neuronal death
HD Treatment

• Symptoms
  – Motor: DA depleting agent, neuroleptics also stabilise mood abnormalities
  
  – Cognitive: No real treatment
  
  – Psychiatric: treat for depression eg SSRIs, tricylic antidepressants
  
  – Mood swings: atypical neuroleptics eg sodium valproate
Experimental therapies

“Repair” Therapies
- growth factors e.g. CNTF, GDNF
- cell transplantation
- stem cells
- primary fetal striatal tissue

“Disease Modifying” Therapies
- e.g. iRNA
- CoQ10
- Rapamycin

Principal Site of Cell Pathology
Huntington’s Disease: Summary

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<td>Neurodegeneration of caudate nucleus in basal ganglia, as well as of cortical neurons</td>
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<td>3. Huntington gene</td>
<td>Autosomal dominant, gain-of-function mutation with &gt;40 CAG repeats</td>
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<td>4. What initiates neurodegeneration?</td>
<td>A number of theories…</td>
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