Huntington’s disease

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1872 George Huntington published description

1972 Venezuela cohort

1993 Huntington gene and protein

2003 EHDN founded

2015 Pubmed Reports For HD

2016 George Huntington centenary
Cognition

The single factor most predictive of loss of independence

What do patients and relatives complain about?
Poor concentration, forgetfulness (although formal memory testing usually unimpaired.....
Can’t make decisions.....
Poor judgment.....
Start to fail at complex tasks – cooking a meal etc....
Speech – less rich, lose spontaneity, eventually language deficits.......
May fail early in high level employment.......

- Dysexecutive syndrome – disconnection of basal ganglia and frontal lobes
- With disease progression - cortical degeneration
- Social cognition
  Thompson and Snowden,
- Linguistic abnormalities
  Neuropsychologia 2010 - core deficit may be ability to automate cognitive tasks and use cognitive strategies
- New assessment tools
Behavioural Phenotype

”He can’t make decisions any more... even about the simplest thing like what he wants to drink.... he can wash and dress himself, but only if I nag him. He just sits in front of the TV all day. We don’t have conversations anymore - he doesn’t ever have anything to say”.

“I’m always treading on egg shells and no matter what I do she turns on me and she can get quite nasty. She smokes and drinks, which she didn’t do before. My daughter has moved out to live with her grandfather. This is tearing us apart”

Behavioural phenotype
- Apathy
- Irritability
- Perseveration
- Loss of empathy
- Depression, anxiety,
- Delusions/hallucinations rare

From Craufurd et al
Circadian rhythms and sleep

Progressive sleep and electroencephalogram changes in mice carrying the Huntington’s disease mutation

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Are non-CNS systems affected?

Characterization of Gastric Mucosa Biopsies Reveals Alterations in Huntington’s Disease

Citation

Una Jones, Monica Busse, Stephanie Enright and Anne E. Rosser

Figure 1: Respiratory function and disease progression in people with manifest Huntington’s disease. a) Respiratory muscle strength and total functional capacity (TFC). b) Lung volume and TFC. MIP: maximal inspiratory pressure; FVC: forced vital capacity.

Use of hand-held dynamometry in the evaluation of lower limb muscle strength in people with Huntington’s disease

Monica E. Busse
Gareth Hughes
Charles M. Wiles
Anne E. Rosser

Personal View

Treating the whole body in Huntington’s disease

Jeffrey R. Carroll, Gillian P. Bates, Juan Steffen, Garren Safe, Sarah T. Teelck

Huntington’s disease is a genetic neurodegenerative disorder with symptoms that are linked to the progressive dysfunction and neuronal death in corticostriatal circuits. The causative gene (mutated HTT) is widely expressed outside the CNS and several peripheral signs of disease, including weight loss and increased proinflammatory signalling, are often seen; however, their importance in the pathophysiology of Huntington’s disease is not clear. Studies in animals have shown that features of the disease involving the CNS, including synaptic loss and behavioural alterations, are susceptible to modulation by treatments that target tissues and organs outside the CNS. Links between peripheral biology and neurodegeneration have also been shown in other chronic neurodegenerative diseases, suggesting that modulation of these peripheral targets can offer new approaches to therapeutic development. Treatments targeted to tissues and organs outside the CNS might therefore substantially improve the quality of life of patients with Huntington’s disease, even in the absence of disease-modifying effects.
Disease onset and progression

- Historically, onset determined by clinical onset motor symptoms
- Cognitive can behavioural can pre-date by decade or more
- Transition from pre-manifest to manifest is gradual - window of months/years
- Relentlessly progressive over approximately 20 years
How is the brain affected?

Predominant and early cell loss in striatum of basal ganglia

Medium spiny neuron MSN
Control Pre-manifest Early-HD

Kind permission S Tabrizi
Supplement motor

Motor cortex

Somatosensory cortex

Prefrontal cortex

Putamen

Nuc. acc

Globus Pallidus: Internal

Globus Pallidus: External

Substantia nigra: Compacta

Substantia nigra: Reticulata

Precentral motor area

Supplementary motor area

Premotor cortex

Corticostriate fibers

Ventral lateral nucleus

Centromedian nucleus

Subthalamic nucleus

Thalamus

Putamen

Supplement motor

Dorsolateral prefrontal

Lateral orbitofrontal

Medial orbitofrontal

Putamen

Caudate

Caudate

Caudate

Nuc. acc

GP/SN

GP/SN

GP/SN

GP/SN

Thalamus
Management of HD: current status

• No disease-modifiers
• Information and support
• Chorea – tetrabenazine, new generation antipsychotics, benzodiazepines – most patients have limited benefit
• Standard psychiatric medication for depression and psychosis, serotonin uptake blockers for irritability
• Physiotherapy – international guidelines available
• Speech and swallow
• Predictive testing – UK guidelines
• Involve in research
40 or more repeats
36-39 intermediate

**Toxic gain of function**
The “Central Dogma” of Molecular Biology

DNA → RNA → Protein

Adapted from Rosant et al. RCS 2012

Slides with permission from Anne Smith
Ionis Pharmaceuticals

Adapted from Rosant et al. RCS 2012
Antisense Oligonucleotides (ASOs)
Do Antisense Drugs Decrease Huntingtin mRNA and Protein Levels?

DNA → ASO → mRNA → Protein → Disease

**mRNA**

**Protein**

**ASO-treated mice**

Weeks post-treatment termination

BACHD animals treated with 75μg/day ASO for 14 days

Kind permission; Anne Smith, Ionis
Do Antisense Drugs Affect the “Disease” in Mouse Models of HD?

ASO Treatment in HD Mice

- Improves motor coordination
- Improves activity
- Decreases anxiety
- Delays loss of brain mass
- Improves survival

Motor Coordination

Latency to fall (s)

Healthy mice, saline
HD mice, ASO
HD mice, saline

Age (Months)

Kind permission; Anne Smith, Ionis
Status of First IONIS-HTT$_{Rx}$ Clinical Study

• Intrathecal ASO vs placebo
• First dose in Sept 2015, closed Nov 2017
• Preliminary headline result – dose-dependent lowering of CSF huntingtin

Next stage – development work for phase III

Not allele specific
Hunt for modifiers of disease-onset

*CAG repeat is a poor predictor of age at onset*
Genome-wide association study to look for gene-modifiers of age of onset

HD modifier GWA results (GeM MOA) are available at HDinHD.org

- At least three regions (one on chr 8 and 2 on chr 15 were associated with earlier than expected age of onset
- Enriched signals on networks of DNA repair genes
How could this relate to HD?

Post mitotic somatic CAG expansion – more pronounced in striatum
Relationship to DNA repair mechanisms?
Potential therapeutic target.
**Aim:** circuit reconstruction

**Key concept:** donor cells must be of a genuine MSN phenotype
NEST-UK fetal tissue transplant trial

- 5 patients-bilateral striatal implants
- Follow up using CAPIT-HD
- Stereotaxic implantation
- General anaesthesia
- Immunosuppression - 1 year

Ethically approved
Fetal tissue bank

PAPER
Unilateral transplantation of human primary fetal tissue in four patients with Huntington’s disease: NEST-UK safety report ISRCTN no 36485475

A E Rosser, R A Barker, T Harrower, C Watts, M Farrington, A K Ho, R M Burnstein, D K Menon, J H Gillard, J Pickard, S B Dunnett, for The NEST-UK consortium
New fetal tissue transplant studies: TRIDENT addressing critical issues

20 patient followed using CAPIT-HD (Core Assessment Protocol for Intracerebral Transplantation in HD) protocol

3-5 patients to receive bilateral striatal deposits of fetal ganglionic eminence, mid-late 2018

• Substantially **higher numbers of cells** transplanted

• Duration of immunosuppression increased

*Pave the way for direct delivery of new therapeutics to brain*
Working towards pluripotent cells for clinical application: Repair-HD mission

To establish all the components necessary to take human pluripotent stem cell derived neuronal cells through to the point of ‘first-in-man’ clinical trial in Huntington’s disease (HD).
New treatment available now: exercise/training

- Significant increase in fitness
- Significant improvement in motor score