Huntington’s Disease 101

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Huntington’s disease

- Adult onset
- Juvenile onset
- Diagnosis and treatment
- Basic science breakthroughs
- Translational research
HD Basics

• Autosomal dominant --- there is a 50/50 chance of a child getting the disease if a parent has it.

• HD does not skip generations--If a person with an affected parent escapes the disease, so will all of their children.
HD Basics

- HD is a trinucleotide repeat disorder. (other repeat disorders include: Fragile X, Myotonic dystrophy, Kennedy’s, SCA I, Machado-Joseph, etc)

- Individuals with > 37 CAG (poly glutamine) repeats express the HD phenotype.

- Repeat sizes from 27-36 are considered unstable for future generations. There is a tendency for “anticipation” when the gene is transmitted by the father.

- There is a rough correlation between repeat size and age of onset.
Normally $< \sim 10-27$ CAG repeats


In HD there are more than 36 repeats

Onset: 31-68 yrs
37 year difference in age of onset.

Onset: 4-26 yrs
22 year difference

68 Repeats
43 repeats

37 year difference in age of onset.
HD Basics

• The disease starts insidiously and progresses continuously.

• Symptoms include changes in:
  – Behavior
  – Motor function
  – Cognitive function
In Adults Motor Symptoms Include:

Chorea
Motor impersistence
Oculomotor changes
Impaired fine motor control
Balance and gait disorder
Dystonia
Speech/swallowing problems
Behavioral Symptoms Include:

Obsessive compulsive disorder
Depression/mood swings
Poor impulse control
Psychosis
Anxiety
Intellectual Difficulties In HD

- Completing complex tasks
- Organizing and prioritizing
- Adapting to change
- Problem solving
- Creative thinking
- Word finding
- Memory
HD is a progressive neurological disorder

Be prepared to adapt.
HD affects many aspects of how a person functions. However, it does not do so to the same degree and at the same rate in every person.
It’s not going to progress predictably like this!

- Normal
- A bit of a problem
- A big problem
- A major problem
Being Prepared.

Establish a relationship with a physician and/or support group and/or therapist early on. Build a local community support network.
Lifestyle Adaptations

• Changes in job performance.
  – Move to lower level, less stressful positions
  – Part-time work
  – Volunteer positions
  – Expand hobbies
Lifestyle Adaptations

• Driving.
  – Safety is the first priority
  – Alternate forms of transportation
  – Plan ahead when relocating.
  • Near bus routes
  • Near community assistance
Lifestyle Adaptations

• Finances.
  – Plan ahead
  – Power of attorney
  – Long-term care plans
Lifestyle Adaptations

• Environment and Domestic Issues.
  – Simplify
    • Limit distractions
    • Avoid visual and auditory clutter
  • Establish routines
    – Household aides
    – Assisted living
Caregiver Survival

• Team Approach. The more help the better.
• Schedule time for yourself.
  – Make this a priority.
  – Make this a routine and stick to it.
• Arrange for a backup caregiver on a regular basis.
• Use Humor.
  – Rent funny movies.
  – Laugh at yourself and HD.
• Change your expectations for success.
• Relaxation techniques.
  – Yoga, Hot Baths, Meditation, Old Movies, Whatever works for you.

(Adapted from: Jane Paulsen, Understanding Behavior in HD 1999)
Juvenile HD

- Usually a family history of relatively young onset HD.
- Often inherited from the father. (~80%).
- CAG repeat size usually greater than 60.
Juvenile HD symptoms

- Stiffness of legs. Scissoring gait.
- Walking on toes.
- Clumsiness of arms and legs.
- Decline of mental ability and milestones.
- Changes in behavior.
- Seizures (~ 25% of children with HD).
- Swallowing and speech difficulties.
- Bradykinesia.
- Cerebellar signs.
A functional scale for assessing juvenile-onset HD

- A. School attendance.
- B. Academic/developmental performance.
- C. Chores.
- D. Activities of daily living.
- E. Residence.
Dangers of premature testing

- Incorrectly blaming symptoms on HD.
- Discrimination (insurance, future employment).
- Negative psychological and social effects.
- Testing of children is discouraged.
Genetic testing choices.....
When to get tested and why...or why not...

Genetic counseling and making well informed decisions.
HD Treatment:
This is a progressive disorder. Treatment plans need to be regularly reviewed.

- Currently no medicine or specific treatment advised for everyone.

- Symptomatic treatment
  - **Chorea.** Benzodiazepines, amantadine, neuroleptics, valproate, tetrabenazine
  - **Spasticity/rigidity.** PT/OT, benzodiazepines, baclofen, dantrolene, tizanidine.
  - **Speech/swallowing** and dental care issues.
  - **Behavior.** Depression, Aggression, OCD, Impulse control
  - **Gait and balance issues.** Canes and Walkers often problematic.
  - **Seizures** rare in adults but can be relatively drug resistant.
Gait and balance disorders.

Very little data on type of gait disorders, rate of progression or effectiveness of interventions. Commonly recommend repetitive exercises, Tai Chi, Yoga.

Problems learning new skills (also OCD)

Often have difficulty with canes and walkers.

Problems with motor impersitence.

(Reverse hand brakes or regular hand brakes)
Research Advances in Huntington’s Disease

• A….Laboratory research:
  – Animal models of HD (mice, zebra fish, fruit flies).
  – Cell culture studies.
  – High through-put studies.
• Results of recent clinical trials.

• B….Ongoing Clinical trials:
  – Observational
  – Interventional
    • Symptomatic treatment
    • Neuroprotective, restorative.
Huntingtin is normally a cytoplasmic protein.
Normal Huntingtin
Mutant Huntingtin
Normal Huntingtin

Mutant Huntingtin
Some promising agents.

- Coenzyme Q10
- Ethyl-EPA
- Trehalose
- Minocycline
- Creatine
Examples of some of the numerous recent advances in HD basic science research.


Allele-specific silencing of dominant disease genes

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Edited by Charles M. Radding, Yale University School of Medicine, New Haven, CT, and approved April 9, 2003 (received for review February 17, 2003)

PNAS 100: 2003

Molecular Medicine for the Brain: Silencing of disease genes with RNA interference. Davidson and Paulson, March 2004 Lancet Neurology
A randomized, placebo-controlled trial of coenzyme $Q_{10}$ and remacemide in Huntington’s disease

The Huntington Study Group*

Coenzyme Q10
(antioxidant and cofactor in mitochondrial function)

Remacemide
(noncompetitive NMDA receptor antagonist)
347 HD patients followed for 30 months
Four treatment groups:

Coenzyme Q 10  (300 mg twice a day)
Racemide
Coenzyme Q10 + Racemide
Placebo
Conclusions: Neither treatment significantly altered decline, however Coenzyme Q10 showed a trend towards slowing of disease progress. BUT…….(HSG, Neurology, 2001)
Other potential beneficial agents

• Prozac (fluoxetine)
• Depakote (valproic acid)
• Lithium
• Namenda

• Physical exercise (may increase BDNF) and mental exercise.
Research Advances in Huntington’s Disease

• Laboratory research:
  – Animal models of HD (mice, zebra fish, fruit flies).
  – Cell culture studies.
  – High through-put studies.

• Clinical trials:
  – Observational
  – Intervenotional
    • Symptomatic treatment
    • Neuroprotective, restorative.
Why participate in a clinical trial?

• Advance medical science. HD is a rare disease. We have so many new therapies coming up, we need everyone to help us find the best.

• Earlier access to new therapeutic interventions.

• Free medications.

• Increased interactions with specialists and support staff.
Types of Trials

- **Observational** -- learning more about the disease.
- **Interventional** -- trying to slow the disease process down and searching for a cure.
Disadvantages of participating in clinical trials

• You might get the placebo.

• Potential risks of new and untried therapy.

• Time commitment.
The number of potential treatments keeps growing……

Coenzyme Q10
Phenyl Butarte
Exercise
Ethyl-EPA
SSRIs

Gene Therapy
siRNA
Creatine

Stem Cells
BDNF
GDGF
CNTF

Chocolate
Caspase -6 Inhibitors
Trehelose
Dimebon

Ampakinis
Memantamine
Minocycline

Ursodiol (bile acid)
Curcumin
On the path to a cure.....
Resources for patients and families

www.HDSA.org
www.huntingtonproject.org
www.huntington-study-group.org
wwwhdlighthouse.org