Huntington Disease 101

What IS Huntington Disease and what should I know?

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Presenter Disclosures

Suman Jayadev

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose or list
George Huntington in 1868
“Over fifty years ago, in riding with my father on his professional rounds, I saw my first case of ‘that disorder’, ... It made a most enduring impression upon my boyish mind, an impression every detail of which I recall today, an impression which was the very first impulse to my choosing chorea as my virgin contribution to medical lore.

We suddenly came upon two women, mother and daughter, both tall, thin, almost cadaverous, both bowing, twisting, grimacing. I stared in wonderment. What could it mean? My father paused to speak with them and we passed on.

Then my medical instruction had its inception. From this point on, my interest in the disease has never wholly ceased.”
George Huntington’s 1872 paper “On Chorea” in the Medical and Surgical Reporter

Communications.

ON CHOREA.

BY GEORGE HUNTINGTON, M. D.,
Of Pomeroy, Ohio.

Read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872.

Chorea is essentially a disease of the nervous system. The name “chorea” is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the
In the last 150 years

1950s: Doctors observed a high occurrence of HD in a Venezuela community, Lake Maracaibo

1983: Genetic Marker for Huntington Disease found

1983: Huntington Disease Society of America formally begins

1993: Huntington Gene and CAG expansion identified (and reported in the New York Times!)

1996: Huntington mouse model developed
Huntington Disease Clinics today

HDSA has helped to provide framework of HD care and support
HD Patients and their Team

Docs
Neurologists, Geneticists, Psychiatrists, Primary Care

Nurse

Genetic Counselor

Social Worker

Physical, Occupational therapies
Huntington disease the basics

- Inherited in an “autosomal dominant” manner
- Typically the disease first manifests in 30’s to 50’s
- Range of onset is 1yr to 90+
- Typical features are motor, psychiatric and cognitive
- The disease course is progressive
- Infrequently the gene change can transform dramatically and lead to earlier HD in offspring (anticipation)
- Juvenile HD (JHD) appears differently in children
Autosomal Dominant Inheritance

- HD Gene
- Working copy
The gene change causing HD
Repeat of “CAG” in the DNA sequence of HD gene

Chromosome
Each chromosome contains many genes

Gene
A gene is a segment of DNA that codes for a protein
CAG expansion in gene sequence causes longer gene and protein
CAG Repeat Ranges

- **Normal**: will not develop HD
- **Intermediate**: will not develop HD, small chance of passing down larger repeat
- **Reduced penetrance**: may or may not develop HD
- **Full penetrance**: will develop HD at some point in lifetime
- **Juvenile HD**: affects children and teens

# of CAG Repeats in the gene

- 10-26
- 27-35
- 36-39
- 40-Above
- 60-Above
There is a very rough correlation of CAG repeat and age of onset

Keum et al 2016
Multiple factors influence Age of Onset

- CAG repeat number only explains 50-70% of the variability of age of onset
- There are other genes that may modify onset and progression
- Maintaining healthy life habits can be helpful
Symptoms of HD

Psychiatric

Cognitive

Motor
Symptoms of HD

- “Executive Function”
- Problem solving
- Multi-tasking
- Mental inflexibility, getting stuck on things, shifting attention
- Slowness of thought
- Difficulty learning new skills
- Lack of insight into deficits
- Impulsivity
Symptoms of HD

- Depression
- Irritability, bad-temper outbursts
- Apathy, Emotional blunting
- Perseveration
- Mania
- Psychotic symptoms (hallucinations, delusions, paranoia)
- Aggressive behavior
- Increased risk of suicide
- Challenges with alcoholism/drug use
Symptoms of HD

- Chorea – jerky, involuntary movements
- Dystonia – twisting, contracting of body, limbs, face
- Eye movements changes, slower
- Changes in speech
- Difficulty swallowing
- Slowness of movement
- Stiffness
Anticipation
Increased severity and earlier age of onset

Age at onset

- 42 yr 48 CAG
- 47 yr 48 CAG
- 48 yr 46 CAG
- 52 yr 46 CAG
- 13 yr 65 CAG
- Unaffected 16 yr old
Juvenile Huntington Disease

• Disease looks different in kids with HD
  – Seizure
  – Increased stiffness, slowness of movement
  – Loss of cognitive milestones
  – Tremor
• Most often (around 80%) inherited from an HD father where expansion has increased dramatically
• Disease course is faster
• Associated with having CAG repeat >60
• 5% of HD is diagnosed before age 20 yrs
Progression of HD over lifespan
How could HD impact our lives

Early and Moderate

- Increased friction at home or at work because of irritability or mood changes
- Difficulty with learning new challenging tasks at home, work or hobbies
- Clumsiness – fidgety
- Less motivation to engage socially
- Depression
- Sexual dysfunction, maybe a new development impacting dynamics with others

Medications can be useful for depression, irritability and movements

Some employers will consider accommodations at work

Have open communication at home about changes in mood and interactions

Make plans to stay socially engaged if that’s helpful
How could HD impact our lives

As the disease progresses

- Increased movements impair driving, safety going up and down stairs, in and out of bathtub
- More intrusive behavior/psychological changes may appear – delusions, paranoia, obsessive thoughts
- Worsening cognitive changes leads to needing to leave work, may need help with household chores
- Will need assistance from disability, insurance to supplement income

Medications can assist with psychiatric symptoms and movements
Engage with social workers early to discuss disability, getting Occupational/Physical therapy early to evaluate home safety
Have frank discussions about when to stop driving
Consider activities such as volunteering, day programs to stay engaged
How could HD impact our lives

Later in disease

- Safety while walking has become an issue
- Progressive difficulty with speech impairs communication
- Even with assistance at home, may not be able to stay at home and move to adult family homes or higher levels of care eventually
- Movements may be difficult to control despite multiple medications

Continue to work with physical, occupational and speech therapies to evaluate for safety and swallowing safety
Your HD team can communicate with facilities regarding non-pharmaceutical interventions, as well as medications
How could HD impact our lives
Later in disease

- Metabolic changes and other reasons may cause significant weight loss
- Difficulty with swallowing safely may lead to aspiration and pneumonia
- It may be difficult to get sufficient food by my mouth

Work with your team to discuss high calorie diets
Patient may have preferences about what they’d like to eat and balance with known risks
Discuss how do we want end of life care to look like
Remember to seek support for the entire family in addition to patient
HD causes brain cell injury, eventual loss of certain brain cells and shrinkage of brain regions.
HD affects different regions of the brain AND the connections between them.
The abnormal HD protein accumulates within neurons in the brain.

Neuron is a brain cell.
How does Huntingtin cause cell damage?

Normal HD protein

Expanded HD protein

Other genes
Generating Energy
Protein processing
Recycling cell components, moving proteins through neuron
Many dynamic areas in HD research!

**Biomarkers**

- ![Biomarker chart](chart.png)

**Living with HD**

- ![Living with HD illustration](living.png)

**Gene silencing**

- ![Gene silencing diagram](silencing.png)

**Stem cell derived brain cells**

- ![Stem cell image](stem_cells.png)

**Clinical Trials**

- ![Clinical trials image](clinical_trials.png)
What the researchers are working on

- Need to more about how the HD form of Huntingtin causes cell damage
- What are the normal functions of the Huntingtin protein?
- What other pathways in the brain impact progression of disease? (such as inflammation)
- And does that suggest additional opportunities for drug approaches?
- What are additional biomarkers we can use to quantify disease onset and progression?
- How can we get medicines across the “blood brain barrier” so that we can give them through blood
Questions?
Sustained reduction in mutant Htt mRNA and protein by transient ASO infusion into the CNS

Huntington gene RNA

Huntington protein
Sustained benefit from transient ASO infusion into brain of HD mice for 9 months

9 months post treatment with ASO

Coordination

Exploring
Transient gene lowering leads to sustained slowing of disease progression in mice
HD affects different regions of the brain.