The Kids-HD and the Kids-JHD Program

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Presenter Disclosures

Peg Nopoulos

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

No relationships to disclose or list
The Huntington Gene

• Gene is Huntingtin or \textit{HTT}
• Triplet repeat or trinucleotide repeat

\texttt{CGCCTAATCATGGCTCAGCAGCAGCAGCAGCAGCAGGATATCCG}

• Normal variation of repeat
  ➢ 10-35
• >40, full penetration for disease
  ➢ Mutant form = \textit{mHTT}
Huntington’s Disease (HD)

Longer CAG repeat → earlier HD onset

Longer repeat = more severe mutation
The Huntington Gene

• Since the discovery of the gene, many studies

• What have we learned?

• An important region of the brain called the striatum is particularly affected in HD

• Large studies of pre-HD subjects like PREDICT and Track have shown that the striatum is affected YEARS before the onset of the disease
Questions that remain

- How far back does the abnormality in the striatum go? Is it possible that it didn’t develop correctly?
- Why are there no symptoms until later in life even though the striatum is abnormal for years before that?
- We became interested in studying how the brain develops in people who have the expanded gene.
Normal Neuron  
Normal Development  

Classical Concept: Gain of Function

Normal Neuron  

Disease process  
(toxic mHTT)

Degeneration

Cell Death

Mutant Neuron  
Abnormal Development

Developmental Concept: Loss of Function

Mutant Neuron

Maturational Processes
• Aging
• mHTT

Disease process is abnormal development

mutant steady state  
made possible by compensation

Degeneration

Cell Death
**Kids-HD Program – Who is Eligible**

- Subjects are children / young adults ages 6-25 years who
  - Have a parent (or grandparent) with HD (at-risk)
  - Healthy controls from the community = y
  - No symptoms of HD (no diagnosis of JHD)

- For Research purposes only, DNA from blood or saliva is used to measure CAG repeats in HTT; 2 groups:
  - Children at risk who are gene non-expanded (GNE)
  - Children at risk who are gene expanded (GE)

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**Kids-JHD Program – Who is Eligible**

- Subjects are children / young adults ages 6-25 years who
  - Have already been diagnosed with JHD
They come to Iowa City
Kids-HD and Kids-JHD Programs

- Magnetic Resonance Imaging (MRI) allows us to take a picture of a person’s brain
- We get volumes of specific brain regions
- We call this assessment of **brain structure**

- We look at **brain function** by looking at thinking skills tasks (memory, concentration, etc.) and motor function
### The Kids-HD Program

<table>
<thead>
<tr>
<th></th>
<th>Combined Controls (CC) (n=356)</th>
<th>At-Risk GE (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (s.d.) / Range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>13.3 (3.8) 6-23</td>
<td>13.9 (4.0) 6-25</td>
</tr>
<tr>
<td>CAG Repeats</td>
<td>20.3 (4.1) 11-34</td>
<td>44.5 (5.1) 36-58</td>
</tr>
</tbody>
</table>

CC= healthy controls and GNE
Effects of GE on Brain Development

- HTT affects development of the striatum
- The higher the CAG the lower the volume

In people with HD, the average CAG length is around 45

Caudate + Putamen = Striatum

Normal HTT
GNE – will NOT develop HD

Abnormal HTT
GE – Will develop HD

Abnormal HTT
GE – Will develop JOHD
The Kids-HD Program

• So if the striatum is abnormal, why are these kids not having any symptoms?

Developmental Concept: Loss of Function

• Maturational Processes
• Aging
• mHTT

mutant steady state
made possible by compensation

Degeneration

What other parts of the brain might be responsible?
Invokes one of the most important advances in neuroscience: circuitry
What happens when your striatum doesn’t develop properly?

The Cerebellum and Striatum are interconnected.

- They develop as a balanced circuit
- When one part is weak, the other part helps out or ‘compensates’
Circuitry

- Theory – abnormal growth of the striatum is compensated for by the cerebellum

![Normal Growth balanced circuit](image)

![Abnormal growth, Cerebellar compensation](image)
• Whhaaaa? The cerebellum involved in HD?
  ➢ the one area of the brain discussed the least in all literature
  ➢ considered to be ‘spared’ by HD disease pathology
Abnormal Development of Striatum

CAG = 10 - 39
Normal Function

CAG = 40 - 44
Abnormal development with initial cerebellar compensation
CAG 40-44, well compensated; very subtle abnormalities in childhood
Adult onset of symptoms

CAG = 45 - 59
Abnormal development
Cerebellum doesn’t compensate 100%
abnormalities in thinking and motor skills during childhood; the higher the CAG the worse the skills
Adult onset of symptoms, but earlier

CAG > 60 (JHD)
Severe abnormal development
cerebellum enlarged
Cerebellum instead of helping, is now ‘over-active’
An over-active cerebellum leads to the hypokinetic symptoms of JHD (slowing, stiffness)
Juvenile Huntington’s Disease

- Prevalence – How Common is it?
- Clinical features
- The diagnostic challenge
Juvenile Huntington’s Disease

- Prevalence – How Common is it?
- Clinical features
- The diagnostic challenge
Juvenile Huntington’s Disease

• Rare
  – Best estimate is around 5% of all HD cases
  – Even more rare for childhood onset
Genetic Anticipation

When HTT is passed on from parent to child, there is a chance it will expand.

Example:
- Parent: CAG = 43
- Child: CAG = 65

This expansion is more likely to happen when the parent is MALE.

- Most JHD cases (up to 90%) have a father with HD
- Converse – vast majority of fathers with HD will NOT have a child with JHD
Juvenile Huntington’s Disease

- Prevalence
- Clinical features
- The diagnostic challenge
Clinical Features

• Like all forms of HD, symptoms cluster in 3 main categories
  – Motor symptoms
  – Cognitive symptoms
  – Behavioral symptoms
Motor Symptoms

- Bradykinesia – slowing of movements
- Rigidity – stiff muscles
- Dystonia – muscles contract in abnormal position
- Ataxia – slow, shuffling, stooped walk
- Dysarthria – slurred speech
- Tremor
- Masked face – lack of movement in face
- Chorea – dance-like movements
Motor Symptoms

• These symptoms are often referred to as ‘Parkinsonian’ as they are similar to features of Parkinson’s disease.

• Chorea is much less common than is seen in adult onset HD, and often comes later in the disease
Cognitive Symptoms

- Everything from general intelligence (IQ) to specific functions such as memory, attention, language and visuospatial skills

• For children with childhood onset (before the age of 10), this may be a failure of thinking skills development

• For JHD it is often seen as declining school or academic performance

• Like Adult onset, these thinking skills deficits will progress over time
Behavioral / Psychiatric Symptoms

- Behavior can be divided into 2 main categories:
  - Externalizing Behaviors – behavior that other people can see
    - Hyperactivity
    - Inattention
    - Opposition (not wanting to follow rules, talking back)
    - Aggression
  - Internalizing Behaviors – what people feel inside
    - Sad or depressed
    - Anxious
    - Obsessions
Behavioral /Psychiatric Symptoms

- Externalizing – the most common
  - Attention Deficit Hyperactivity Disorder (ADHD) may be diagnosed
  - Aggression may come on quickly, with unclear triggers
- Psychosis: hallucinations and delusions
  - More common in onset in teens and 20’s
In a large study of 53 cases (Siesling et al.)

- 70% presented with Behavior symptoms
- 48% with motor symptoms
- 27% with cognitive symptoms
- During the course, the number of cases that experienced behavioral disturbances:

  - Males: 93%
  - Females: 81%
Other Accompanying Features

• Seizures
  – Up to 30-40% of cases
    • Generalized or tonic-clonic - “grand mal”
      – Lose consciousness; entire brain involved
    • Partial complex
      – Impaired consciousness; parts of the brain involved
    • myoclonic epilepsy
      – Muscle jerks, no impairment of consciousness
      – Tend to be more common in the earliest onset cases and can be a presenting symptom
Common but unrecognized

- Through social media, we administered a survey designed to quantify identified symptoms often mentioned by JHD caretakers, but not part of the classic triad motor, cognitive, behavioral symptoms

1. Sleep Disturbance
2. Pain
3. ‘Itching’
4. Tics
5. Psychosis
## Common but unrecognized

<table>
<thead>
<tr>
<th>Demographic Info</th>
<th>N=33</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis (yr)</td>
<td></td>
<td>12.21</td>
<td>3-21</td>
</tr>
<tr>
<td>Current Age (years)</td>
<td></td>
<td>15.75</td>
<td>4-27</td>
</tr>
<tr>
<td>CAG repeat length</td>
<td></td>
<td>36.09</td>
<td>15-100</td>
</tr>
</tbody>
</table>

![Bar chart showing the percentage of individuals experiencing different symptoms:](chart.png)

- Sleep Disturbance: 87%
- Tics: 78%
- Pain: 69%
- Itching: 60%
- Psychosis: 39%
Duration of Disease

- Somewhat controversial
- Duration of disease in JHD does NOT seem to be any different than duration of disease in adult onset
  - Average 15-20 years from diagnosis to death
- Thus even though CAG repeat can predict age of onset, it does NOT seem to predict duration of disease
Juvenile Huntington’s Disease

- Prevalence
- Clinical features
- The diagnostic challenge
Juvenile Huntington’s Disease

• Onset
  – The presence of unmistakable (not subtle) neurologic (motor) signs
The Diagnostic Challenge

• Average length of time from first symptom to diagnosis – NINE YEARS *(Ribai et al)*

• *Most common presenting symptom is behavior*
Behavior is a non-specific symptom

- Data from Kids-HD study
- Parent ratings of behavior
  - **AO** = aggression / opposition
  - **HI** = Hyperactivity / inattention
  - **DA** = Depression / anxiety

  The higher the score, the worse the behavior

  \[
  GNE = \text{at risk, Gene Non-Expanded}
  \]

  \[
  GE = \text{at risk, Gene Expanded SHORT CAG 40-49}
  \]

  \[
  GE = \text{at risk, Gene Expanded LONG CAG 50-73}
  \]

- Behavior does NOT distinguish groups
  - Exception being more depression in the gene non-expanded group
The Diagnostic Challenge

• What is the risk of getting a genetic test based on a non-specific symptom?
  – That symptom may not be related to HD
  – Analogy – making diagnosis of pneumonia for every patient that presents with a cough

• Example, child with ADHD
  – Genetic test: CAG=43
  – What if motor symptoms do not develop
    • And behavioral symptoms ameliorate
    • May have gotten ‘presymptomatic’ testing on a child who did not have the chance to make that decision for themselves
Can MRI imaging help the diagnosis of JHD?

- Here are 5 Seven year old females
- Which one has JHD, age onset 6, CAG 101?

A ‘clinical’ scan, read by a radiologist – qualitative assessment: does this brain ‘look’ different?
No – this will not help diagnosis
QUANTITATIVE MRI

- Computer program calculates volumes
- JHD case compared to 7 age matched females, healthy controls

Healthy Control Mean = 0

ICV Cortex White matter Caudate Putamen Thalamus Cerebellum

Healthy Control Mean = 0

Putamen

Caudate
Acknowledgements – Nopoulos Lab

Front: Amanda Benavides, Joel Bruss, Corinne Hamlin, Jessica Lee, Stephen Cross, Lynsday Harshman, Gail Harmata, Jon Goodwin

Back: Sasha Tereshchenko, Eric Axelson, Ian DeVolder, Peg Nopoulos, Jennifer Henderson, Jordan Harrelson, Sonia Slevinski

Not shown: Vince Magnotta,
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