HDSA Annual Convention June 2015

Diagnosing Juvenile Huntington’s Disease (JHD)

Peg Nopoulos, M.D.

Professor of Psychiatry, Neurology, and Pediatrics
University of Iowa, Iowa City, Iowa
The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the 2013 HDSA Convention program is for informational use only.

HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.
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

Huntington’s Disease Society of America
Juvenile Huntington’s Disease

Peg Nopoulos, M.D.
Professor of Psychiatry, Neurology and Pediatrics
University of Iowa, Iowa City, Iowa, USA
Juvenile Huntington’s Disease

- Genetics
- CAG repeat length and age of onset
- Prevalence
- Clinical features
- The diagnostic challenge
Juvenile Huntington’s Disease

- Genetics
- CAG repeat length and age of onset
- Prevalence
- Clinical features
- The diagnostic challenge
DNA is the ‘code’ for genes

- Genes code for a protein. Proteins work in the cell and eventually direct the formation of a trait (eye color)

- The code for genes is made up of 4 ‘nucleotides’
  - T  A  G  C

- This is the ‘dna alphabet’

- Example of a code for a gene:
  - TTAGCGTAGCC
The Huntington Gene

- Is named Huntingtin (**HTT**)
  - Has a section where 3 nucleotides are repeated = trinucleotide repeat or ‘triplet’ repeat.
  - Every human has these repeats
    - Three nucleotides make up an amino acid
    - Strings of amino acids make up a protein

**GGTCAGAGGGGATCATTAGCTACAGCAGCAGCAGCAGCAGCAGTTGATA TCCGG**
The Huntington Gene

- When the repeat is 40 or greater, then the gene is called mutant $HTT$ or $mHTT$
  - When CAG is greater or equal to 40, then Huntington’s Disease (HD) will develop
  - Onset and diagnosis of HD is average age of 40 years of age
- When the diagnosis of HD is made at age 21 or before = Juvenile Huntington’s Disease or JHD
Juvenile Huntington’s Disease

- Genetics
- CAG repeat length and age of onset
- Prevalence
- Clinical features
- The diagnostic challenge
Juvenile Huntington’s Disease

• Onset is defined as
  – The presence of unmistakable (not subtle) neurologic (motor) signs
The number of CAG repeats is related to the age of onset

AGE of Onset

10 20 30 40 50 60 70 80

CAG REPEAT

>100 > 60 > 50 40-49 36-39

**CAUTION – these are estimates; about ½ of JHD cases are <60 repeats**
Juvenile Huntington’s Disease

- Genetics
- CAG repeat length and age of onset
- 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

- Genetics
- CAG repeat length and age of onset
- 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
• A common accompanying feature is seizures or epilepsy
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
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

– often comes later in the disease
Cognitive Symptoms

• Cognitive Skills = Thinking skills
  – 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

– **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
Presenting Symptoms

• 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
Duration of Disease

- Somewhat controversial
- Duration of disease in JHD does NOT seem to be much different than duration of disease in adult onset
  - Average 15 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

- Genetics
- CAG repeat length and age of onset
- Prevalence
- Clinical features
- The diagnostic challenge
The Diagnostic Challenge

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

• Most common presenting symptom is behavior

  – BUT DIAGNOSIS IS NEVER MADE BASED ON BEHAVIOR
The Diagnostic Challenge

• What is the risk of getting a genetic test based on a non-specific symptom?
  – Behavioral problems are common
  – That symptom may not be related to HD
• Example, child with ADHD but no motor symptoms
  – Genetic test: CAG=43
  – So onset of symptoms likely to be in adulthood – this is NOT JHD
  – However, now this child has the knowledge that they have the expanded gene
    ✓ This may be psychologically difficult for many reasons
Kids-HD Program

- Study of brain structure (using Magnetic Resonance Imaging or MRI) and brain function (thinking or cognitive tests, motor tests, ratings of behavior)

- Subjects are children ages 6-18 years who
  - Have a parent with HD (at-risk)
    - NO symptoms – preHD children (no JHD)
  - Have no family history of HD (controls)

- For Research purposes only, DNA from blood or saliva is used to measure CAG repeats in HTT; 3 groups:
  - Children at risk who are gene non-expanded (GNE)
  - Children at risk who are gene expanded (GE)
  - Healthy controls
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** = at risk, Gene Non-Expanded
- **GE** = at risk, Gene Expanded SHORT CAG 40-49
- **GE** = 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

- Can we do anything to make the diagnosis earlier?
- *Can we provide doctors with tools that will allow them to make the decision to get the gene test sooner?*
Kids-JHD Program

• Study of brain structure (using Magnetic Resonance Imaging or MRI) and brain function (thinking or cognitive tests, motor tests, ratings of behavior)

• Subjects are children ages 6-18 years who
  – Have been diagnosed with JHD
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

- Currently done for research
- Computer program calculates volumes
- JHD case compared to 7 age matched females, healthy controls
QUANTITATIVE MRI
• Also could look at CHANGE OVER TIME
• In a span of one year, is the volume of the caudate/putamen shrinking compared to a healthy control?
• If so, this could also provide evidence to the doctor even though motor symptoms haven’t started yet

![Graph showing volume change over time for JHD and control groups.](image)

- JHD
- Control

Time 1  1 year later

Putamen
Caudate

Huntington’s Disease Society of America
The Diagnostic Challenge

• Maybe QUANTITATIVE MRI can be used to provide the doctor with better information so they will feel more comfortable in ordering a gene test even when motor symptoms are not present or significant
Acknowledgements – Nopoulos Lab

Front Row: Jane Brumbaugh, Amanda Benavides, Christina Saenz, Thomasin McCoy, Jessica Lee, Amy Conrad, Jessica Forbes.

Back Row: Carrie Heald, Andrea Aerts, Peg Nopoulos, Sonia Slevinski, Michael McHugh, Nick Baker, Sasha Tereschencko, Ian DeVolder
Questions & Discussion