Diagnosing Huntington’s disease
Current recommendations and pitfalls
Presenter Disclosures

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

No relationships to disclose or list
Juvenile Huntington's disease

- Autosomal dominant, Triplet repeat,
- CAG expansion of HTT gene: trinucleotide repeat
  - Special testing that is not seen in common high resolution chromosomes or even microarray testing
- < 10 percent of patients, present before the age of 20 years.
- Normally, we have 10-26 repeats, in HD>36 CAG repeats
Huntington disease genetics

- Chromosome 4p16.3
- Expanded CAG repeat
  - Excess glutamine
- Huntingtin gene
Huntington gene

Huntington’s disease gene

Triplet

The gene’s DNA is translated into amino acids which form the abnormal huntingtin protein.

Glutamines

Possible “polar zipper” effect

HAP-1
Juvenile onset HD

• Higher incidence if inherited from the father
  – Instability during spermatogenesis
• Usually, younger onset in family members
• Higher repeat size, the earlier the manifestation
• >60 (abnormal if more than 40)
Juvenile HD

- Historical perspective
  - Huntington first described in 1872
  - Hoffman in 1888: female, aged 36 who was diagnosed with epilepsy at the age of 2 to 3. Began to have poverty of movements. She had a first cousin and was believed that mother transmitted the disease.
  - Bruyn suggested definition at 20 years

- Quarell et al 2013
Juvenile HD

- Meta-analysis
  - High income in nations: 4.81%
  - Middle income: Venezuela and South Africa: 9.95%
  - 20% had childhood onset?
Huntington’s disease: FAQ

• What is my child’s risk?
• Is the behavior problem a symptom?
• Are the movements interfering with daily activities?
• Are the movements a sign of HD?
  – Tics
  – Obsessive compulsive
  – Behavior
  – Hyperactivity
Diagnostic criteria: childhood onset HD (<10 years)

- A family history of HD (usually in the father) and two or more of:
  - Declining school performance
  - Seizures
  - Oral motor dysfunction
  - Rigidity
  - Gait disturbance

- Nance and US Huntington Disease Group
Dangers of premature testing

• Incorrectly blaming symptoms on HD.
• Discrimination (insurance, future employment, others).
• Negative psychological and social effects.
• Testing of other children in the family is not encouraged.
• Disease modifying/prevention
  • Mother once told me that she had more years with her child.
Dangers of premature testing

- In very adolescents or young adults, dangers of social and academic goals
- Limitations of employment
- Self esteem
  - Mood disorders
  - Suicide rate is high

- 44 subjects
- Of the 15 presenting under age 10, 12 had CAG repeats greater than 80.
- Symptoms included declining school performance, seizures, oral motor dysfunction, rigidity and gait disorder.
- Presenting symptoms in those over age 10 were more varied but usually included behavioral and motor symptoms.
Juvenile HD testing

- Athens, Greece, 76 patients with symptoms suggestive of HD with disease onset <20 years
- Mean age of onset: $14.0 \pm 5.4$ years with lower age of onset in paternally inherited disease ($12.4 \pm 5.6$) and maternally inherited $17.9 \pm 1.7$ years.
- Most prevalent: rigidity, dystonia, behavior and cognitive dysfunction, followed by chorea, epilepsy and ataxia
- In negative cases: tremor, athetosis, tic, spasticity and depression
- Conclusions:
  - Symptomatic children with (+) family history
  - Highly unlikely if no family history

  » Koutsis, Katadima et al March 2013
JHD

- 76 patients; 24 were positive
  - Rigidity (21%)
  - Dystonia (21%)
  - Behavioral change (16.7%)
  - Cognitive dysfunction (12.5%)

- Infantile
  - Dystonia and Rigidity

- Adolescent
  - Cognitive, Rigidity and Behavioral changes
Juvenile Huntington disease

• Different presentation compared to adults
  – Stiffness/ Rigidity rather than Chorea
  – Cognitive decline
  – Behavioral disturbance
  – Seizures
Motor manifestations

- Rigidity
- Stiffness
- Clumsiness
- Walking up on toes: progressive rather than very early on
- Ataxia
- Bradykinesia
- Chorea in only 10% of cases and only in adolescent
Motor manifestations

• Other reasons for walking up on toes
  – Cerebral palsy (premature children)
  – Dopa responsive dystonia
  – Autism
  – White matter disease: Leukodystrophy
Symptom management

• Stiffness/Rigidity:
  – Botulinum toxin
  – Baclofen: side effect: sleepiness
  – Benzodiazepenes: valium
  – Physical therapy: stretching/ strengthening
    • Daily
  – Occupational therapy

Long term issues: PAIN
Symptom management

• Dystonia/Rigidity
  – Levodopa
  – Dopamine agonists: Ropinarole, Bromocriptine and Pramipexole
  – Anticholinergic agents: tremor: Trihexyphenidyl or Benztropine

*Balancing act because some medications for behavior may cause worsening of movement disorder.
Behavioral problems

• Depression
• Obsessive compulsive behavior
• Irritability
• Aggression and Impulsiveness: young teens
  – Very difficult to distinguish from teenagers
  – May seem normal to physicians when we meet them
  – Teacher and Parental accounts of behavior
Cognitive decline

• Learning disability
  – May cause behavior problems
• ADHD
• ADD
• Language issues
Cognitive problems

- Cognitive testing by developmental psychologist to assess strengths and weaknesses
- Speech and Language disorders
  - Communication devices.
  - Speech therapy
- Behavior problems
  - ADD
  - Impulsivity
Cognitive problems

- Cognitive testing by developmental psychologist to assess strengths and weaknesses
- Speech and Language disorders
  - Communication devices.
  - Speech therapy
- Behavior problems
  - ADD
  - Impulsivity
Sleep issues

• Very minimal information in children but very important for overall health
  – Iron deficiency
  – Sleep onset problems
  – Impact on seizures, specially sleep deprivation
  – Impact on cognition
Huntington’s disease: Seizures

- Multicenter: 90 subjects
- 38% of subjects, more likely to occur with younger ages of HD
- Seizures types
  - Tonic
  - Myoclonic
  - Staring spells
- Cognitive decline and behavioral changes, Non choreiform movements
- EEG pattern available in 16:
  - multifocal, rarely generalized.

Cloud et al 2012
Juvenile HD

- Weight Loss
  - High calorie
  - PEG tube
- Poor oral hygiene
  - Nursing care
- Aspiration pneumonia
  - Swallow study
- Pain
  - Difficult to assess, end of life.
Natural history of HD

• Onset
  – Mean age of onset: 39
  – Range: 2 to 80 years

• Duration
  – Mean survival: 19 years
  – Typical range: 15 to 25 years
Families: Why do you need to know?

• Planning for the future
• How much time do I have left?
• How do I correct his behavior if he can’t help it?
• Adopted families want to know
  – Bias?
How to diagnose

• Simple but not so simple
  – HD gene triplet repeat: not available as a usual chromosome testing
  – Counseling by a multidisciplinary team
  – Counseling by geneticists
Antiepileptic medications

• Older AEDS
  – Carbamazepine
  – Phenobarbital
  – Phenytoin
  – Primidone
  – Valproic Acid

• Newer AEDS
  – Lamotrigine
  – Levetiracetam
  – Oxcarbamezepine
  – Gabapentin
  – Topiramate
  – Zonisamide
  – Felbamate
  – Tiagabine
Partial seizures

- Super new medications
  - Lacosemide (Vimpat)
    - Slow sodium channels
  - Clobazam (OnFi: benzodiazepene)
    - GABA
  - Rufinamide (Banzel)
    - Sodium channels
Symptom management

Partial onset seizures

- Carbamezepine
- Oxcarbamezepine

Generalized seizures

Keppra: behavior
Lamictal
Valproic acid (Depakote)
Topiramate
Zonisamide
Behavior management

- Counseling
- Cognitive therapy
- Resources in community
- Medication
  - Guafenesin for hyperactivity
  - Stimulants for hyperactivity
  - SSRI’s for depression
A functional scale for assessing juvenile-onset HD

- A. School attendance.
- B. Academic/developmental performance.
- C. Chores.
- D. Activities of daily living.
- E. Residence.
C. Chores.
- 2- Able to assist in age-appropriate manner with household chores.
- 1- Occasionally assists with chores.
- 0- Unable to participate in household chores.

D. Activities of daily living.
- 3- Performs self-cares in an age appropriate manner.
- 2- Requires some assistance for bathing, dressing, grooming, or feeding.
- 1- Assists others who bathe, dress, or feed him/her
- 0- Unable to assist in self care.
E. Residence.

- 2- At home with only family assistance
- 1- At home/group home/foster care with assistance from non-family members.
- 0- Living in a skilled nursing care facility.

Add points to determine stage of HD

- **Stage 1** ............ 11-13 points
- **Stage 2** ............ 7-10 points
- **Stage 3** ............ 3-6 points
- **Stage 4** ............ 1-2 points
- **Stage 5** ............ 0 points
A. School attendance

3- attends school, no special needs.
2- attends school, some regular classes, some modified classes.
1- attends school, few or no regular classes.
0- unable to attend school.

B. Academic/developmental performance

3- Reading/writing/math skills appropriate to age.
2- mild decrease in academic performance but still able to take a test or write.
1- unable to write legibly but able to communicate orally.
0- unable to read/write/communicate orally.
JHD educational resources
Pamphlet for families can be downloaded from Huntington’s Disease Society of America Web site (www.hdsa.org)
HDYO

• Huntington's Disease Youth Organization

• hdyo.org

• HDYO! A site created for young people to learn about HD in an age-appropriate, friendly and factually correct manner.
International JHD Resources

PUBLICATIONS

*Juvenile Huntington's Disease* (and other trinucleotide repeat disorders), Quarrell, Brewer, Squitieri, Barker, Nance, Landwehrmeyer, 2009 (Amazon.com Price:$110.00) Mostly geared towards professionals.

WEBSITES

EHDN – [www.euro-hd.net](http://www.euro-hd.net)
JHD section [www.euro-hd.net/html/network/groups/jhd](http://www.euro-hd.net/html/network/groups/jhd)
Other Websites with JHD Resources

Stanford HOPES (Huntington’s Outreach Project for Education at Stanford) – JHD section created 2010 [www.stanford.edu/group/hopes/cgi-bin/wordpress/category/hd-basics/juvenile-hd/](http://www.stanford.edu/group/hopes/cgi-bin/wordpress/category/hd-basics/juvenile-hd/)


MDVU (Movement Disorders Virtual University) [www.mdvu.org/](http://www.mdvu.org/)
(primarily for health care providers)

Patient Power, JHD interview with Martha Nance and Sandra Kostyk, 2008 [www.patientpower.info/program/juvenile-huntingtons-disease](http://www.patientpower.info/program/juvenile-huntingtons-disease)

HD Lighthouse ([www.hdlf.org/jhd](http://www.hdlf.org/jhd))
HDSA PUBLICATIONS (con’t)

**JHD SPECIFIC**

The *Family Guide Series to Juvenile HD* by Martha Nance, MD (copyright 2009)

*The Juvenile HD Handbook* by Martha Nance, MD (copyright 2009)

*School and the Juvenile HD Experience* (copyright)

*The JHD Directory* (copyright 2009)

HDSA Webinars (archived on [www.hdsa.org](http://www.hdsa.org))

**GENERAL**

Palliative and End of Life Issues November 17, 2010

HD and Nutrition January 26, 2011

Team Management of HD February 22, 2011

Communication through Use of Assistive Technology September 26, 2011

**JHD SPECIFIC**

Juvenile HD February 24, 2012
International JHD Resources

Scottish HD Association (www.hdscotland.org/youth)
  JHD Section divided by audience
This site is mostly geared to helping those in the following groups deal with having a family member with HD
  Children Ages 8-12
  Teens Ages 13-17
  Young Adults Ages 18-25
  Professionals (very limited info for health care providers.)

Australia (www.ourhdspace.org)
Website dedicated to helping young people affected by HD