HD Across the Lifecycle

HSG Family Day
November 8, 2019
Panel members

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Huntington’s Disease

Progressive, hereditary degenerative neuropsychiatric disease

Prevalence estimated 1 - 13/100,000 world-wide

Estimated prevalence in US:
32,000 people with HD
220,000 at-risk
2000 new cases annually

Symptoms: Motor, cognitive, behavioral disorders

Dr. Nancy Wexler in Venezuela with juvenile HD patient
Who gets Huntington’s disease?

- **Autosomal dominant inheritance** with high penetrance
- **Age at onset typically 30’s – 40’s but can range from 2 – 85.**
- **Anticipation:** may arise earlier in those paternal inheritance
- **5 - 10% of cases arise in families without a history of HD – late-onset**


HD world-wide prevalence = 2.71/100,000
Prevalence in US and Europe = 10-13/100,000
HD prevalence in Asia = 0.4/100,000
HD is caused by an expansion in the number of CAG repeats in the huntingtin (HTT) gene.

Huntingtin gene (HTT) → huntingtin protein

### CAG repeat length

<table>
<thead>
<tr>
<th>Condition</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>&lt; 26</td>
</tr>
<tr>
<td>Unstable</td>
<td>27 – 35</td>
</tr>
<tr>
<td>Reduced penetrance</td>
<td>36 - 39</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>&gt; 39</td>
</tr>
<tr>
<td>Juvenile HD</td>
<td>&gt; 60, but sometimes less</td>
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</tbody>
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HD Collaborative Research Group *Cell* 72:971–983
Relationship between CAG repeat length and age at onset


- The higher the CAG repeat length, the earlier the age at onset
- CAG repeats between 36 – 39 have reduced penetrance and older age at onset.
- Repeats > 60 typically cause juvenile onset HD
Symptoms in Huntington’s disease

- Motor
  - Chorea, dystonia, loss of voluntary motor control
- Cognitive
  - Difficulty with attention, organization, planning, multi-tasking
- Psychiatric/behavioral
  - Depression, high risk of suicide, anxiety, many others
- Other:
  - Weight loss, pain, bowel and bladder dysfunction
- Death after 15-20 years
Adult-onset HD

- Symptoms begin most often in 30-40s
- Symptoms are initially mild but become progressively worse over time
  - Hyperkinetic motor symptoms (chorea) in early stages
  - Develop more hypokinetic motor symptoms (dystonia, bradykinesia)
  - Balance and gait disturbance
  - Apathy progresses with disease
  - Irritability and depression are related to functional decline
Prodromal HD

• Subtle motor, cognitive, and psychiatric changes can be detected up to 10-15 years before diagnosis
Juvenile Onset HD (JoHD)

Juvenile onset HD is defined as symptom onset before age 21
- Only 5-10% of cases of HD have juvenile onset
- Only 1-2% of cases have childhood onset, defined as onset before age 10 years

The features of JHD are different than those in adult onset.
- **Instead of chorea**, children/teens have rigidity and stiffness of muscles
- **Cognitive changes** and school/learning issues are prominent
- **Mood changes** also occur
- **Seizures** occur in 25%
- **Oral** motor dysfunction
- **Behavioral** disturbances
- **Faster** rate of progression and death

*Fusilli C et al, Lancet Neurology 2018*
Juvenile Onset HD (JoHD)

• Inheritance:
  • More likely to occur with inheritance from father (75%)
  • Anticipation
    • The CAG repeat length is “mutable” in spermatozoa and may increase from one generation to the next
    • This can also occur with maternal inheritance, but is less likely

• Usually, one parent is known to have
  • In childhood-onset HD, sometimes the child may develop symptoms before their affected parent
Late onset HD (LoHD)
European Huntington’s Disease Network Registry

• Patients > 60 years old compared to those with younger age at onset (30 – 50 yrs)
• Late onset seen in 11% of 6007 HD patients in the Registry study.
• CAGn was 40.8 in LoHD compared to 44.4 in age 30 - 50
  • 14% had 36 - 39 CAG repeats vs 0.02% in those aged 30 – 50
• 76% had a family history of HD, vs 95% in younger group
• More likely to present with gait and balance difficulties as initial symptom
• Rate of disease progression was similar to younger patients

HD across the Life Cycle

McCoglan P and Tabrizi SJ. Huntington’s disease: a clinical review.
Panel Discussion