Updates in Huntington’s Disease
AL Academy of Neurology 2017
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Updates in HD 2017

• The UAB / HDSA Huntington’s Disease Center of Excellence
  • Updates, what are we up to?
  • Genetic testing in HD
• Updates on Symptomatic Treatment Options
• Research for a Cure!

Worldwide Prevalence of HD

Average 4-7/100,000
US: ~30,000 total patients
Alabama: ~300 total patients
Mississippi: ~200 total patients
Thanks to my Multidisciplinary Team!!
UAB / HDSA Center of Excellence

UAB / HDSA Center of Excellence
• Currently following ~185 patients with Huntington’s disease
• Monthly multidisciplinary clinic
  • Each patient sees PT, OT, ST, psychiatrist, neurologist, social worker
  • Only my visit is billed, all other care paid through CoE grant

Updates on Diagnosis of HD
• Traditional: chorea (or other HD symptom) plus consideration of family history then confirmation by gene test
• 3 patients this year with chorea, no FHx of HD, age >75, gene test positive for HD
• When/how to get the gene test?
  • Symptomatic testing
    • Simple in-office counseling, then direct order of gene test
    • UAB does NOT perform gene test so must use outside lab
    • Not covered by Medicare or Medicaid
    • Athena: $1200, Baylor: $450, Emory: $400 ($300 with UAB discount)
Updates on Diagnosis of HD

- Presymptomatic testing
  - Despite availability, only 5% of those at-risk choose to test
  - UAB HD Clinic offers:
    - FREE initial genetic counseling by phone
    - Anonymous and FREE neurology evaluation
    - Only cost to the patient is gene test itself
      - Can test under a pseudonym if patients prefer
  - To access this, please DO NOT refer the patient via usual vehicles but instead call our clinic directly (205-996-2807) and we will set this up for the patient!

Clinical Presentation of HD

- Average age of symptom onset is 30’s-50’s
- Socioeconomic impact of loss of prime productivity years
  - By then, many have had children
- Loose correlation of CAG repeat length and symptom onset/severity

Clinical Presentation - “HD Triad”

- Motor
  - Most common (90%) is chorea – effects on gait, coordination, speech, swallowing
  - Can also consist of tics, dystonia
  - Slowing of smooth pursuit/saccades
- Cognitive
  - Executive dysfunction progressing to full dementia
- Psychiatric/Behavioral
  - Most common: Depression/OCD (30-80%)
  - Impulsivity and Suicide risk
  - Irritability, Apathy, Personality change

Gusella, et al 2014
Updates on Symptomatic Treatment of HD

- No cure but myth of “nothing we can do”
- Symptomatic Therapy
  - Chorea:
    - Deutetrabenazine (Austedo) – FDA approved 4/2017
    - Tetrabenazine (Xenazine) – FDA-approved 2007
      - Now generic, 3 makers, still primarily specialty pharmacy, gross cost is $90,000/year (branded Xenazine was $120,000/year)
      - Typical and atypical (not quetiapine/clozapine) antipsychotics – off-label, very little data
      - Amantadine - Used by some, but very little data
      - Benzodiazepines - Again, limited data; Can worsen gait/falls
    - DBS – a few case-series, have not done this yet at UAB

Updates on Symptomatic Treatment of HD

- Other Non-Motor Symptoms
  - Depression/Anxiety: often responds even better to SSRIs/SNRIs, etc. than traditional depression
  - Perseveration/Impulsivity/Irritability: Mood stabilizers (valproate, oxcarbazepine)
  - Delusions: Typical or atypical antipsychotics
  - Cognition: No proven pharmacotherapies, so no utility for cholinesterase inhibitors or memantine (all studied and failed)

Tetrabenazine for HD

- VMAT-2 Inhibitor, FDA approved for HD chorea

**Change in TMC From Baseline**

![Graph showing change in TMC from baseline with statistical significance](https://example.com/graph.png)
Tetrabenazine for HD

- Symptomatically suppresses chorea of all etiologies
- My success stories
- Can have problematic side effects
  - Increased bradykinesia/parkinsonism
  - Sedation
  - Akathisia
  - Depression

Deutetrabenazine for HD

- Deuterium-substituted tetrabenazine changes PK profile, allows similar efficacy with less (50%) total daily dose of drug

Deutetrabenazine vs. TBZ

- Caveat – NOT a head-to-head study, but...

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Placebo (n=120)</th>
<th>Deutetrabenazine (n=105)</th>
<th>p-value</th>
<th>Placebo (n=120)</th>
<th>Deutetrabenazine (n=105)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8.8% (11/120)</td>
<td>1.1% (1/105)</td>
<td>0.0000</td>
<td>6.6% (8/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
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<tr>
<td>Dry mouth</td>
<td>3.3% (4/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>2.5% (3/120)</td>
<td>0.0% (0/105)</td>
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<tr>
<td>Headache</td>
<td>4.2% (5/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>3.3% (4/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
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<tr>
<td>Insomnia</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
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<tr>
<td>Erythema</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>0.8% (1/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
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<td>Fatigue</td>
<td>9.2% (11/120)</td>
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<td>0.0001</td>
<td>7.5% (9/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
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<tr>
<td>Infusion site reactions</td>
<td>0.0% (0/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
<td>0.0% (0/120)</td>
<td>0.0% (0/105)</td>
<td>0.0001</td>
</tr>
</tbody>
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TBZ and TBZ are substrates of the United Human Health Initiatives (UHHI)}
Logistics of Ordering TBZ and Austedo

- How to order tetrabenazine now that it has gone generic?
- TAGI pharmaceuticals through variety of different pharmacies (QuickRx)
- PSR Form for Austedo
- What about for inpatients?

Current Scientific Approaches – Search for a Cure

Gene Silencing

- In mice, switching off mHtt allows recovery of neurons
- Gene silencing technologies (goal is lowering mHtt expression)
  - Zinc finger proteins (ZFP)
  - Small interfering RNA (siRNA)
  - Antisense oligonucleotides (ASO)
AntiSense Oligonucleotides

Lu and Yang 2012

Antisense Oligonucleotides

- Phase 1b safety study began late 2015! (Ionis-HttRx)
- Efficacy of ASO will NOT be determined in this trial
- Ionis-HttRx is an ASO that lowers normal and mutant huntingtin
- Duration of action ~ 4 months
- Drug to be delivered intrathecally
- Due to complete Sept. 2017
  - No major safety events thus far...
  - 36 patients + placebo controls
  - 4 doses (10, 30, 50 and 70 mg)
  - 14 week study at clinical sites in UK, Germany and Canada only
  - Post-treatment observations up to 29 weeks

WAVE LifeScience ASO

- WSE-120101 will be an ASO that targets the single nuclear polymorphism (SNP) rs362307
- Attempt to be allele-specific silencing
**WAVE LifeScience ASO**

- Similar to Ionis-HTTRx, will require infusion via spinal tap
- Small initial study (Mass. General, Vanderbilt, Johns Hopkins) for safety to commence late 2017
- Subjects will first have SNP sequenced, and based on presence of SNP 1, 2, or both, will be entered into appropriate study.
- ~60-75% of HD patients should be eligible

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**Gene Editing: Zinc Finger Proteins/CRISPR**

- ZFN’s create double stranded breaks in DNA at specific points
  - Requires creation of custom targeted DNA sequence
- Clustered regularly interspaced short palindromic repeats (CRISPR)
  - Combines existing defense mechanism against viral invasion with RNA guide to target and excise DNA sequences (ie could shorten a 42 to a 22)
- uniQure developing AAV5-miRNA model to knockdown mHtt production
  - Would require only single dose
Gene Silencing Challenges

- Delivery and Distribution
  - Since treatments do not cross BBB into the brain, how to deliver?
  - Even delivered directly into CNS, hard to get into areas most affected by HD
- Allele-selective silencing
  - What are effects of suppressing normal Htt?
  - How to just turn off the mHtt but leave normal Htt on?
- Side effects?
- Which patients to treat?

Take Home Message

- HD is a difficult disease due to its inheritance pattern and ability to devastate entire families
- BUT there is hope
  - Treatments (that really work) NOW
  - Exciting things on the horizon...
  - Annual HD Education Day, UAB Alumni House, 9/16/17
- Send us your HD patients!!
  Jenna Smith, RN, Clinic Coordinator: 205-996-2807