Huntington’s disease

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Outline

• History
• Clinical features
• Genetics
• Pathogenesis
• Treatments

HD overview

• Autosomal dominant inheritance
• Gene mutation, huntingtin (htt) gene, short arm 4th chromosome (Chr 4p16.3)
• Expanded CAG repeats
• Exon 1 of htt gene
• Adult onset, rare juvenile
• Mean duration 17-20 years
• Clinical triad
George Huntington (1850-1916)

- On Chorea (1872)

- Described cardinal features
  - Adult onset
  - Hereditary
  - Abnormal movements
  - Behavioral issues
  - Progressive

On 12 June 1806, in the long-established farming and fishing village of East Hampton, at the far eastern end of Long Island, about 60 miles northeast of New York City, USA, Captain David Hedges, a member of the local gentry, awoke to find his wife missing. A search ‘thro fields of grain to the shore’ did not find her ‘and there is every reason to believe she has precipitated herself into the surf’, reported the local newspaper. ‘Mrs. Hedges was about 40 years of age, and was much esteemed by her neighbors’ the obituary continued. ‘This extraordinary step is attributed to her extreme dread of the disorder called St. Vitus’ dance, with which she began to be affected, and which her mother now has to a great degree. From some arrangements of her clothing it appears she had for some time contemplated her melancholy end.’ (The Suffolk Gazette, 30 June 1806).
Genetic History of HD - Seminal events

- 1972 - Centennial celebration of Huntington’s paper
- Venezuela project – description of HD families around Lake Maracaibo in Venezuela
- 1979 – First American expedition to Maracaibo
- 1983 - Discovery of location of genetic marker (Gusella et al., 1983)

Epidemiology

- Prevalence estimates vary across the world
  - ~7-10 cases per 100,000 in White populations
    - Less in Black and Asian populations
  - 2.3-17.4/100,000 in USA (~1/7300)
  - 560/100,000 (Moray Firth, Scotland)
  - 700/100,000 (Lake Maracaibo, Venezuela)
- Incidence ~1/10,000; approx 30,000 in US
- Founder effects in some populations
- Increased prevalence over past 2 decades with increased availability of genetic testing

HD – Clinical triad

MOTOR

PSYCHIATRIC

COGNITIVE

Motor

- Chorea
- Oculomotor abnormalities (impaired saccades)
- Dystonia (cranial, cervical, truncal, limb, bruxism)
- Tics or “tourettism”
- Myoclonus
- Bradykinesia
- Rigidity
- Gait difficulty, postural instability, ataxia
- Motor impersistence, with dropping things, dipping gait
- Dysarthria
- Dysphagia
- Juvenile phenotype - dystonia, parkinsonism, myoclonus
Psychiatric

• Dysphoria, agitation, irritability, apathy, anxiety (> 65%)

• Frequent symptoms (20-50%)
  • Disinhibition
  • Depressed mood
    • Depression > mania
    • Suicide (5-10% > general population)
  • Euphoria
  • Aggression

• Infrequent (5-12%)
  • Delusions, compulsions

• Rare (<5%)
  • Hypersexuality, hallucinations

Cognitive

• “Subcortical dementia”
• Executive function
  • Poor planning, organizing, flexibility, adapting to alternatives
• Processing speed
• Memory
• Verbal fluency
• Visuoperceptual and construction
• Judgment

• Affect functional independence (esp. processing and attention/initiation deficits)
• MCI in ~38% of prodromal HD on standardized assessments
HD progression

Reilmann et al., 2014

Lifecycle

Walker 2007
Juvenile HD

- Westphal variant
- Age of onset < 20
- 5-10% of HD cases
- AD but typically paternal transmission
- Initial features – personality changes, parkinsonism, bradykinesia, rigidity, dystonia
- Other – leg stiffness, scissoring gait, toe walking, clumsiness, decline of mental function and milestones, behavioral changes
- Later features – dementia, dysarthria, abnormal eye movements, tremor, ataxia, myoclonus, seizures
- Less chorea
- Duration of illness 5-15 years
- CAG repeats > 50

HD – Genetics

https://www.geneticsupportfoundation.org/autosomal-dominant-inheritance
## CAG Repeat Lengths

<table>
<thead>
<tr>
<th>CAG Repeat length</th>
<th>Interpretation</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;27</td>
<td>Normal</td>
<td>• No disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No known risk to children</td>
</tr>
<tr>
<td>27-35</td>
<td>Intermediate (normal, mutable)</td>
<td>• No symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Small risk to children with expansion</td>
</tr>
<tr>
<td>36-39</td>
<td>Reduced penetrance (abnormal)</td>
<td>• May or may not have symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 50% risk to children</td>
</tr>
<tr>
<td>&gt;39</td>
<td>Full penetrance (abnormal)</td>
<td>• Symptoms</td>
</tr>
</tbody>
</table>

### HD – Age of onset and CAG repeat length

![Age of onset vs CAG repeat length](Walker2007.png)
Intermediate alleles (27-35 repeats)

- Case reports
  - Autopsy proven HD with 29 CAG repeats
  - Late onset – 82 year old with 2 year h/o chorea (CAG 29)

- Prospective Huntington At Risk Observational Study (PHAROS)
  - 50/983 (5.1%) had intermediate alleles (IA) 27-35 repeats
  - IA were similar to controls (<26 CAG) on UHDRS motor, cognitive, and functional measures
  - IA were worse on behavioral scores, apathy and suicidal ideation than controls

- European registry study
  - 657/12,190 (5.38%) had < 36 CAG with 76 IA carriers (11.56%), 581 controls (88.44%)
  - No sig differences in outcome measures but an effect of age
  - Older IAs had higher chorea vs. controls (p=0.001) and at 1-year, IA carriers had greater cognitive decline (p=0.002)

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CAG repeat transmission

- CAG repeats > 28 show instability on replication
- Most instability leads to expansion (73%)
- Contraction can also occur (23%)
- Greater instability with spermatogenesis
- Greater anticipation with paternal transmission

Kenney et al., 2007; Squitieri et al., 2012; Killoran et al., 2013; Garcia-Ruiz et al., 2016; Cubo et al., 2016
“Sporadic” HD

• No known family history may be as high as 8% of all individuals with HD
• Rare, de novo expansion from nonpenetrant but unstable repeats (27-35 range)
• Other factors:
  • Anticipation (child before parent)
  • Early death or misdiagnosis
  • Adoption
  • False paternity

Genetic modifiers

• GeM-HD consortium
• GWA signals reveal loci that modify the age at onset of HD
• Effects at the chr15 locus hasten or delay onset by 6 or 1.4 years, respectively (FAN1, MTMR10)
• A single effect at the chr8 locus hastens onset by 1.6 years (RRM2B, UBR5)
• MLH1 association & pathway analysis implicate DNA handling in disease modification

Tome et al., 2013; Gusella et al., 2015; Hensman Moss et al., 2017; Flower et al., 2019
Women abstaining from drugs delayed AMO by 4.6 years
Abstinence from tobacco delayed AMO by 2.3 years
Imaging

- Striatal atrophy
- Cortical thinning
- White matter atrophy
- DTI changes
- Microglial 11C-PK11195 – increased binding
- Phosphodiesterase 10A (PDE10A) changes

Tabrizi et al., 2011; Niccolini 2014; Aylward 2014; Paulsen et al., 2014; Wilkes et al., 2019

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**Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis**

Lauren M Byers, Filip B Rodrigues, Raj Bhimoo, Alexandra Dore, Blair Elzelev; Raymond A Cironi, Rachel J Scalfi; Sarah Tabrizi; Henrik Zettlitz, Douglas Longley; Edward J Wild

- TRACK-HD (n=366); London (n=37, CSF)
- At any given timepoint, NFL concentrations in plasma correlated with clinical and MRI findings.
- In longitudinal analyses, baseline NFL concentration correlated significantly with subsequent decline in cognition (SDMT; Stroop word reading), TFC, and brain atrophy (caudate, whole-brain, grey matter, white matter, ventricular expansion).
- Concentrations of NFL in CSF and plasma were correlated in mutation carriers ($r=0.868$, $p<0.0001$).
Pathology

• Striatal atrophy with neuronal loss and gliosis
• Caudate > putamen atrophy
  • “Box car” ventricles
• Marked neuronal loss in deep layers of the cerebral cortex, and other basal ganglia, thalamus, cerebellum, to varying degrees

• Affects mediolateral, dorsoventral gradients
  • Input to GPe/SNr before Gpi
• Medium spiny neurons
• Nuclear (INI) and cytoplasmic inclusions (CI) of huntingtin

Management

• Genetic counseling

• Symptomatic treatment
  • Motor
  • Psychiatric
  • Cognitive
  • Dysarthria
  • Nutrition, weight loss
  • Dysphagia

• Psychosocial

• Disease-modifying?
Genetic counseling

- Important role
- Understanding what HD is and means for families
- Predictive testing
- Confirmatory and diagnostic testing
- Absent family history
- Atypical symptoms

Chorea

- AAN guidelines
  - Tetrabenazine (up to 100 mg/day)*
    - Reversibly inhibits vesicular monoamine transporter 2 (VMAT2) → decreased uptake of monoamines and depletion of storage
    - Monitor - depression
    - HSG study 2006
    - FDA approved 2008
  - Amantadine (100-400 mg/day)
  - Riluzole (200 mg/day)
    - Level B for above
  - Neuroleptics (Level U, insufficient)

- Other considerations
  - Depression
  - Psychiatric symptoms
  - Compliance
  - Chorea may “improve” over time

Table 3 Considerations when treating chorea pharmacologically

<table>
<thead>
<tr>
<th>If the patient has troublesome chorea with:</th>
<th>Consider using:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other symptoms</td>
<td>Tetrabenazine, amantadine, (riluzole)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Olanzapine, cannabimoids</td>
</tr>
<tr>
<td>Psychosis, aggression or impulsivity</td>
<td>Aripiprazole, haloperidol, olanzapine, risperidone, or other neuroleptic</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Benzdiazepines</td>
</tr>
<tr>
<td>Depression</td>
<td>Aripiprazole and avoid tetrabenazine</td>
</tr>
<tr>
<td>Apathy</td>
<td>Amantadine or stimulating medications and avoid neuroleptics</td>
</tr>
<tr>
<td>Prominent dystonia</td>
<td>Amantadine, benzodiazepines, focal neurotoxin injection, and avoid neuroleptics</td>
</tr>
<tr>
<td>No response to pharmacotherapy</td>
<td>Deep brain stimulation</td>
</tr>
</tbody>
</table>

Armstrong et al., 2012; Reilmann 2013; Frank 2014
N=90, manifest HD patients
DTBZ (n = 45) or placebo (n = 45)
Titration over 8 weeks, maintained for 4 weeks, followed by a 1-week washout
• Primary endpoint: change from baseline in total maximal chorea score
• Improved total maximal chorea score 4.4 units DTBZ vs. 1.9 units placebo; mean between group difference -2.5 units (p<0.001)
• Significant improvement in patient global impression of change
• AEs – depression, anxiety, akathisia (both groups)
• FDA approved in 2017
• Long-term study (ARC-HD) efficacy and safety, ≥1 year follow up (mean 119 +/- weeks)

Behavior

• Depression, irritability, obsessive-compulsive behaviors
  • Environmental changes
  • SSRI’s or SNRI’s
  • “Typical” or “atypical” antipsychotics
  • Mood stabilizers
  • Irritability SRX246, vasopressin 1a antagonist – 82/106 completed trial; placebo vs. 120 or 160 mg BID; met tolerability endpoint

• Anxiety
  • SSRI’s, benzodiazepines

• Psychosis
  • “typical” or “atypical” antipsychotics

• Apathy
Cognitive impairment

- Cholinesterase inhibitors?
  - Donepezil: randomized, placebo-controlled study (n=30) -> no benefit for cognition, chorea or QoL
  - Rivastigmine: randomized, placebo-controlled, parallel study (n=18) -> no benefit for MCI

- Memantine?
  - Open label, n=12, UHDRS, 3 mos, no benefit for cognition (20 mg/d)

- Adaptations at work/home
- Cognitive-behavioral strategies
- Non-pharmacological

Cubo et al., 2006; Ondo et al., 2007; Sesok et al., 2014

Clinical recommendations to guide physical therapy practice for Huntington disease

Abstract

Objective
In the past decade, an increasing number of studies have examined the efficacy of physical therapy interventions in people with Huntington disease (HD).

Methods
We performed a mixed-methods systematic review using Joanna Briggs Institute (JBI) methodology and included experimental and observational study designs. The search resulted in 23 quantitative studies and 3 qualitative studies from which we extracted data using JBI standardized extraction tools. Results of this review suggested that physical therapy interventions may improve motor impairments and activity limitations in people with HD. Here, we expand on the review findings to provide specific recommendations to guide clinical practice.

Results
We recommend the following specific physical therapy interventions for people with HD: aerobic exercise (grade A evidence), alone or in combination with resistance training to improve fitness and motor function, and supervised gait training (grade A evidence) to improve spatiotemporal features of gait. In addition, there is weak (grade B) evidence that exercise training improves balance but does not show a reduction in the frequency of falls; inspiratory and expiratory training improves breathing function and capacity; and training of transfers, getting up from the floor, and providing strategies to caregivers for involvement in physical activity in the midstages of HD may improve performance. There is expert consensus for the use of positioning devices, seating adaptations, and caregiver training in late stages of HD.

Conclusions
There is strong evidence to support physical therapy interventions to improve fitness, motor function, and gait in persons with HD.

Aerobic exercise +/- resistance training
Supervised gait training
Disease-modifying?

**Negative or mixed results**

- Coenzyme Q10
  - n=609 early stage HD for 60 months (DBPC)
  - No change in Total Functional Capacity score
  - Safe, well-tolerated

- Creatine (CREST-E study)
  - N=553 early manifest HD for 48 months (DBPC)
  - Halted, no effect on functional decline
  - GI side effects
Negative or mixed results

- Pridopidine - “Dopamine stabilizers”
  - HART (North America, n=227)
    - Modified motor score (not significant)
  - MermaiHD (Europe, n=437)
    - Modified motor score (trend) but significant improvements global motor score, eye movements, dystonia, hand movements, gait/balance
  - PRIDE-HD (n=400)
    - Higher doses, longer study, additional outcome
    - Improved TFC but no difference from placebo on total motor score
  - PROOF HD (ongoing)
    - Phase 3, early stage HD

- Laquinimod – immune modulator
  - DBPC trial, 12 months
  - No significant effect on UHDRS-Total Motor score

- SIGNAL clinical trial (VX15/2503 - pepinemab)
  - Monoclonal Ab to semaphoring 4D
  - Regulates activation and migration of inflammatory cells and inhibits differentiation of oligodendrocytes precursors in brain
  - Phase, DBPC trial
  - Late prodromal and early manifest HD
  - Promising neuroimaging data
  - But no significant effect on HD Cognitive Assessment Battery and CGIC

Waters et al., 2018

Therapeutic targets

Wild and Tabrizi 2014; Ross et al., 2014
Genetic-therapeutics?

HTT-lowering strategies

<table>
<thead>
<tr>
<th>Active agent</th>
<th>Mode of delivery</th>
<th>Targeted brain region</th>
<th>Stage of development</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASO nonallele-specific</td>
<td>Intrathecal lumbar infusion</td>
<td>Cortex</td>
<td>First in human trial</td>
<td>Do not cross BBB</td>
</tr>
<tr>
<td>ASO allele-specific</td>
<td>Intrathecal lumbar infusion</td>
<td>Cortex</td>
<td>Preclinical</td>
<td>SNP-based</td>
</tr>
<tr>
<td>RNAi</td>
<td>Viral vector Stereotactic administration</td>
<td>Basal ganglia (putamen)</td>
<td>Preclinical</td>
<td>Do not cross BBB</td>
</tr>
<tr>
<td>Zinc finger proteins</td>
<td>Viral vector Stereotactic administration</td>
<td>Basal ganglia (putamen)</td>
<td>Preclinical</td>
<td>CAG-based</td>
</tr>
</tbody>
</table>
IONIS-HTTRx Phase I

- Gene-silencing clinical trial
- Antisense oligonucleotides (ASO)

- Phase I study - England, Germany, Canada
- Early manifest HD, n=46
- 3:1 ratio to receive HTTRx vs. placebo
- Intrathecal administration, every 4 weeks for 4 doses
- Primary endpoint: safety
- Secondary endpoint: CSF pharmacokinetics

- All patients completed trial (34 vs. 12)
- No serious AEs
- AEs - procedural pain, post-dural puncture HA

IONIS-HTTRx - Phase 3

- IONIS-Roche/Genetech (NCT03761849) – GENERATION HD1
  - RG6042 (tominersen) vs. placebo
  - Evaluate efficacy and safety
  - Manifest HD
  - Multi-center study, world-wide
  - Plan ~900 patients
  - Primary outcome: composite UHDRS and TFC score
  - Intrathecal injections once every 8-16 weeks

- TRIAL HALTED – March 2021

  - Advice of the Independent Data Monitoring Committee
  - Enrolled 791 adults with HD
  - No benefit to patients
  - Participants given tominersen every 16 weeks had similar scores on measures of functional ability, motor function, and cognition, at time points up to 69 weeks (about 1.5 years) of treatment.
  - Participants given tominersen every eight weeks consistently had worse scores than the other two groups.
  - More-frequent dosing also was associated with more severe adverse reactions.
WAVE PRECISION-HD1 and -HD2

- Phase 1b/2a Clinical Trials: PRECISION-HD1 and PRECISION-HD2 in HD
- Evaluate the first allele-specific investigational drugs for HD, WVE-120101 and WVE-120102
- Intrathecal
- Enroll 50 HD patients (Canada, Australia, Europe)
- Early manifest HD with specific SNPs (rs362307 and rs362331)

**TRIAL HALTED – March 2021**
- Participants (n=88)
- Did not lower huntingtin protein levels or NFL
- No significant change in mHTT vs. placebo after single or multiple doses of WVE-120102 and including 32 mg monthly dose
- No dose response level seen
- OLE trial (n=28) with modest reductions in mHTT but inconsistent over course of trial → stopped clinical development of WVE-120102
- Plans for 3rd ASO trial with WVE-003, Phase 1b/2a trial
  - Updated chemical structure

UniQure

- Phase I/II, randomized, multicenter, dose escalation, double-blind, imitation surgery, first-in-human study (NCT04120493)
- AMT-130 in early manifest HD
  - Preclinical studies have shown that AMT-130 lowers huntingtin protein and improved HD signs in animal models
- Safety and Proof-of-Concept Study
- Single administration gene therapy for disease-modification
  - Intrastriatal administration rAAV5-mHTT (low dose, high dose) vs. sham surgery
- First patient enrolled 6/20
- Update 4/21:
  - First 10 US participants successfully dosed (6 with AMT-130, 4 with sham)
Thank you for your attention!

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