Huntington’s & Parkinson’s Diseases: Neurologic & Psychiatric Issues

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Huntington’s Disease

- Typically adult-onset, autosomal dominant disorder characterized by involuntary movements (chorea), dementia, and behavioral changes
- 25,000 affected with HD in USA
- Loss of medium spiny neurons from caudate/putamen
- Chm 4p16.3 CAG repeats

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Friday, September 15, 2017  

**Triad of Symptoms of HD**

- HD is a progressive neurodegenerative disease manifested by:
  - Motor symptoms
    - Chorea
    - Dystonia, parkinsonism, dysarthria, dysphagia, eye movement abnormalities, myoclonus, tics
  - Behavioral symptoms
    - Affective illness, suicide, psychosis, obsessive-compulsive, personality and behavioral changes, sleep disorders
  - Cognitive symptoms
- Chorea is the most visible of the motor symptoms, affecting 90% of patients at some point in their illness.

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**Basal Ganglia**

- Huntington’s disease  
  (loss of medium spiny neurons in striatum:)

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Epidemiology of Huntington’s Disease

Epidemiology of Huntington’s Disease (HD)

- Mean age of onset
  - 30 years\(^1\)
- Prevalence
  - Up to 5–10 per 100,000 worldwide\(^2\)
- HD gene frequency
  - 2.5–3 times higher than clinical disease\(^3\)
- Death
  - Typically, 10–30 years after onset of clinical symptoms\(^4\)

Cause of Huntington’s disease:
The HD gene

Cause of Huntington’s Disease: The HD Gene

- Mutation: CAG repeat counts on the HD gene (IT-15)\(^5\)
- Age at HD onset tends to be inversely correlated to the length of the mutation\(^2\)

Early Huntington’s Disease

- 28 yrs old
- 1 yr h/o falls, dropping things
- 6 month h/o mild chorea

Huntington’s Disease

- 5 yrs later
- Age 33
- 6 yrs after sx onset
Prodromal Issues in HD

- Impaired perception of time. Frequently late, mis-estimate time needed to complete tasks
- Slowing of processing speed. Ordinary mental tasks more tiring and take longer.
- Impaired determination of emotion from facial expression or verbal intonation
- Impaired smell identification, but detection ok.

Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83

Cognitive Difficulty in HD

- Can occur decades before motor symptoms appear.
- Difficulty learning new things and retrieving previously learned information
- Implicit memory (i.e. skills required to ride a bike, play an instrument, drive a car, perform a task) more compromised than explicit memory (i.e. names, dates)
- Attention deficits
- Impaired executive function
- Impaired communication due to dysarticulation, impaired initiation & comprehension of discourse.
- Can have impairment of one’s own actions & feelings

Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83
**Mood-Related Symptoms Common in HD**

- Presymptomatic carriers of *HTT* mutation: higher psychologic stress, irritability, hostility
- Predict-HD study found depression, hostility, obsessive-compulsiveness, anxiety, interpersonal sensitivity, phobic anxiety, psychoticism in *HTT* mutation carriers 10 yrs before predicted onset of motor sx.
- Depression common; 19% w/ MDD; increased risk of attempted/completed suicide


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**Depression is common in HD**

- Past Depression: 50.3% (Patient self-report of seeking treatment for depression)
- Current Depression Factors: 40.5% Sad Mood, 25.0% Low self-esteem, 41.0% Anxiety
- Suicide Attempt: 10.3% (Reported having at least 1 suicide attempt)

N= 2,835

→ Participants were diagnosed with definite HD based upon the presence of motor abnormalities observed during the neurological exam of the UHDRS
→ The study found rates of depression in HD patients were more than twice that found in the general population
  - Depression factors peaked at Stage 2 disease based on TFC


UHDRS=Unified Huntington’s Disease Rating Scale
TFC = Total Functional Capacity
Depression symptoms occur early in HD

- AFFECTED INDIVIDUAL QUESTIONNAIRE (AQ) COMPLETED BY CLOSE RELATIVE OF INDIVIDUAL WITH HD
- ASKED IF AND WHEN A TOTAL OF 19 PHYSICAL, EMOTIONAL, AND COGNITIVE SIGNS OF HD OCCURRED
- MINIMUM 6 YEARS FROM DISEASE ONSET; MEAN AGE AT HD ONSET 41.4 ± 10.2 YEARS


Suicidal Ideation Also Prevalent Pre and Post HD Diagnosis

- Subjects were from the Huntington Study Group database
- Used UHDRS motor section; HD diagnosis confidence level rated from 0–3
- Two scores on neurological exam noted for increase in suicidal ideation
  - Soft neurological signs
  - Possible HD


* With complete data
Cognitive & Behavioral Changes

- Place the greatest burden on HD families
- Most highly associated with functional decline
- Can be predictive of NH placement
- Can be present >15 yrs before motor dx.
- Are highly related to disease specific MRI volume loss

Paulsen JS; Curr Neuro Neurosci Rep (2011) 11:474-83

Medical Treatment of HD

- Motor (chorea): Tetrabenazine, deutetramazine
- Behavioral: antidepressants (sertraline & others), antipsychotics (risperidone, aripiprazole & others), anxiolytics (clonazepam)
- Dementia: consider acetylcholinesterase inhibitors off-label such as donepezil, rivastigmine; and also memantine
Summary for HD

- Cognitive (dementia) and Behavioral decline (irritability, compulsiveness, apathy, poor judgement) are generally more disabling in Huntington’s disease than the motor signs and symptoms.
- Decline of motor control leads to morbidity due to falls, in addition to weight loss from dysphagia and resulting aspiration and resulting infection.
- HD depletes family resources financially and emotionally.

Parkinson’s Disease

- Dr James Parkinson
- 1755 – 1824
- English physician
- Published “An Essay on the Shaking Palsy” in 1817
- Description of 6 patients
**Parkinson’s Disease: Clinical Features**

- Chronic neurodegenerative illness caused by loss of dopamine-containing neurons in substantia nigra
- Cardinal signs: Rigidity, bradykinesia, tremor at rest, postural instability
- Other features: Hypomimia, drooling, hypophonia, micrographia, stooped posture, shuffling gait, retropulsion, festination
- Often asymmetric onset

![Control vs Parkinson’s Disease](image)

**Basal Ganglia – Clinical Correlation**

- Parkinson’s disease (loss of dopaminergic neurons in substantia nigra)
Dopaminergic pathway

- Mesolimbic pathway
- Mesocortical pathway
- Nigrostriatal pathway
- Tuberoinfundibular pathway

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Parkinson’s Disease
### Symptomatic Treatment of Parkinson’s Disease

**Dopamine releaser**
- Amantadine  Symmetrel  100-300 mg

**Anticholinergics**
- Trihexyphenidyl  Artane  2-10 mg
- Benztropine  Cogentin  0.5-8 mg

**MAO-B inhibition**
- Selegiline  Eldepryl, Zelopar  5-10 mg, 1.25-2.5 mg
- Rasagiline  Azilect  0.5-1 mg

**Dopamine agonists**
- Bromocriptine  Parlodel  2.5-40 mg
  (Pergolide)  (Permax)  (0.25-4.5 mg)
- Pramipexole  Mirapex  0.25-4.5 mg
- Ropinirole  Requip  2-24 mg
  (Rotigotine)  (Neupro)  (2-6 mg/24hrs)

### Symptomatic Treatment of PD

**Dopamine precursor**
- carbidopa/levodopa  Sinemet regular  10/100, 25/100, 25/250
  Sinemet ext rel  CR25/100, CR50/200

**COMT Inhibitor**
- entacapone  Comtan  200-1200
- tolcapone  Tasmar  rarely used

**Peripheral Decarboxylase Inhibitor**
- carbidopa  Lodosyn  25 – 150 mg

**Combination**
- carbidopa/levodopa/entacapone  Stalevo  12.5/50/200, 25/100/200
  37.5/150/200
Non-Motor Symptoms in PD include:

- Depression
- Dementia
- Hallucinations
- Sleep difficulty
- Impulse dyscontrol manifested as:
  - pathologic gambling
  - hypersexuality, and
  - other compulsive behaviors.

Neuropsychiatric Symptoms in Early, Untreated PD

- Depression 33%
- Alexithymia 20%
- Anxiety 20%
- Impulsivity 10%

ICDs in early, untreated PD

Minnesota Impulsive Disorder Interview and South Oaks Gambling Scale

- At least 1 ICD 18.5%
- Binge eating 7.1%
- Hobbyism 5.4%
- Punding 4.8%
- Hypersexuality 4.2%
- Buying 3.0%
- Gambling 1.2%
- Walkabout 0.6%  

Impulse Control Disorders in Parkinson’s Disease

- Compulsive gambling, buying, sexual behaviors, eating, punding
- Failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others (DSM-IV-TR)
Possible ICDs

- Change in personality or behavior
- Increased secrecy
- Increased time at hobbies or work
- Decreased need for sleep, or increased insomnia
- Increased medication intake
- Hoarding medications

Stacy (2009). Medicine Reports 1:29

Risk Factors for ICD

- PD dx before age 50
- Dx > 5 yrs
- Male
- Hx/o depression, anxiety, bipolar d/o
- Prior drug/etoh abuse, gambling, other addiction
- FHx of mental illness, drug/etoh addiction
- Dyskinesias
- Levodopa or equivalent > 1000 mg/day
- Dopamine agonist use

Stacy (2009). Medicine Reports 1:20
Cerebral Blood Flow in ICD vs non-ICD Parkinson’s Disease Pts


Impulse Control Disorder: Cross Dressing

- 82 yo WM with PD. Onset age 70 with decreased dexterity at L hand when typing.
- FHx: Sister with schizophrenia. Mom (d) suicide when pt was age 2. Two children.
- SHx: Flew jets in the military. Married for 55 yrs.
- 73: Urge to cross dress since prostate surgery, w/ incr urges since starting PD meds. Ropin 9 mg, selegiline 5 mg, l-dopa 200 mg.
- 73.6: Sees psych for recurr depression. Awakes w/ urge to cross dress.
- 74.1: Psych: urge to wear woman’s clothes, ? rel to mother leaving him (suicide) and having 3 step-mothers as child. Stays active to fight cross dressing urges.
- Age 82: Still has urges to wear women’s undergarments. On l-dopa 900, ropinirole 4, olanzapine 10 (after hospital’n for psychosis, later tapered off), ritalin 10
ICD Case: Compulsive Fishing

- 49 yo WM. Onset PD age 40 w/ sl hand tr, decr L hand dexterity typing.
- FHx: sister bipolar; brother w/ tremor
- SHx: Heavy etoh in college; Navy grad; Married w/2 kids. Executive
- Dxd PD age 41, started pramipexole
- 45: Fishes compulsively “about 1 hr daily”, but says, “I don’t have to every day”. “Not a problem”. On L-dopa 800-1000, pram 3; clonaz 2
- 46: Fishing compulsively. Trip to Brazil to fish.

ICD: Fishing

- Then: Wife discovered he spent $100’s at a strip club when supposedly out all night fishing. Frequent strip clubs in past, now much more often. Wanted to change, reduce PD meds.
- 48.5: Deep Brain Stim (DBS) surgery
- Taking L-dopa 500 to 600, amantadine 200
- Age 49.5: No compulsive behaviors. Home life stable.
ICD Case: Gambling etc.

- 62 yo WM with PD > 10 yrs.
- Age 54: Rotigotine 13.5 mg patch. Some drowsiness when driving without falling asleep.
- Age 55: Drowsy, not falling asleep driving. Rotigotine 18 mg patch, selegiline 10 mg

Case: Pathologic Gambling

- Age 56.2: Enjoyed “recreational gambling” with losses of $50-100. On PD meds, “addiction” to video poker. Losses of $1-2K over hrs. $150-250K over 2.5-3 yrs, mostly video poker. Made excuses for being late so he could gamble. Read about pathologic gambling & DA use while seeing gambling counselor. He noted increased interest in gambling after starting selegiline.
- H/o cross dressing 2-3/ yr since age 6-7. Not previously interfering with his life. Urges to cross dress became overwhelming since fighting the gambling addiction. Pt & wife separated because she was unable to tolerate his behavior.
Case: Gambling etc.

- Moved into appt. Cross dressed daily after work. Obsessive cleaning. Punding: takes apart lawnmower, cleans it, and puts it back together. Compelled to mow his small yard daily. Emotionally labile. SI, no SA or plan. On selegiline, more aggressive betting. On L-dopa 500 mg, rotigotine 18 mg, selegiline 10 mg.
- Age 56.6: Reunited with his wife of 36 yrs who finds his behavior improved & he is “more like he was years ago”.
- No punding. Can concentrate. Still working. Wife working to help w/ debts. Some marital strain due to finances. No cross dressing except briefly a few wkends. No compuls gamblling since stopped rotigot. L-dopa 400

Impulse Control Disorder (ICD)

Treatment

- Recognition of the problem!
- Taper off of stimulants, dopamine agonists
- Treatment with amantadine, antipsychotics
- DBS may permit further reduction of dopaminergic therapy and hence better control of ICD.
Summary for PD

- Both Motor and Non-Motor symptoms are problematic in PD
- Motor symptoms including rigidity, bradykinesias, resting tremor, postural instability
- Non-Motor symptoms include depression, dementia, hallucination, sleep difficulty, and impulse dyscontrol manifested as pathologic gambling, hypersexuality, and other compulsive behaviors.