Bernadette Schoneburg, M.D.

LIVING WITH HUNTINGTON'S DISEASE

Overview

- History
- Background
- Genetics
- Diagnosis
- Treatment
- Resources

Phillips et al. 2008

History

- 1872 - George Huntington described a family from Long Island in his first paper "*On Chorea*"
- 1908 – William Osler said of this paper: "In the history of medicine, there are few instances in which a disease has been more accurately, more graphically or more briefly described."
- 1993 – Huntington gene was identified, located on short arm of chromosome 4

Epidemiology

- The frequency of HD in different countries varies greatly
- Occurs in ~ 1/10, 000 people in US
- Higher prevalence
  - Lake Maracaibo region in Venezuela
  - The island of Mauritius off the South African coast
  - Tasmania

Background

- Huntington's disease is a inherited, degenerative brain disorder
  - Movement
  - Cognition (Thinking, memory etc)
  - Behavior
- Caused by a genetic defect resulting in the loss of cells in a part of the brain called the basal ganglia
- Symptoms onset bw ages 30-50
- Disease duration ~ 20 years

Phillips et al. 2008

Genetics - How do you get HD?

- All people have the Huntingtin gene
  - Gene is made up of a stretch of genetic material (CAG repeats)
- When the length of this repeated section reaches a certain threshold, it produces an abnormal or "mutant" huntingtin protein

# CAG reoeats		
<36	Unaffected	
36-40	Intermediate	+/- symptoms
>40	HD	symptomatic

- Number of CAG repeats inversely correlates with disease onset
  - More repeats = Earlier onset
  - Fewer repeats = Later onset

Phillips et al. 2008

Genetics – continued

- Autosomal dominant inheritance
  - Mutation is passed from parent to child
  - Each child has a 50% chance of inheriting the gene
- Almost always a family member with disease
  - 10 % of HD pts have a (-) family hx
  - Adoption, early death, etc
- Those who inherit the gene will eventually develop the disease
- Those who do not inherit the gene are not at risk
- Must be born with the gene in order to develop this disease

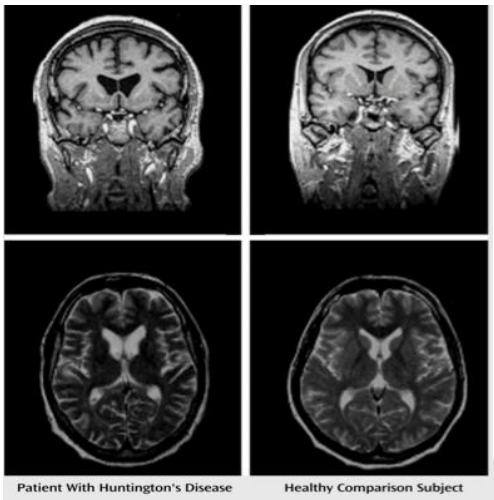
Phillips et al. 2008

Diagnosis

- Clinical
  - Based on thorough history and physical exam findings
- Individuals with a typical clinical exam and genetically confirmed family history
  - Do NOT need genetic testing for dx

Phillips et al. 2008

HD – Imaging



Phillips et al. 2008

Genetic testing

- Readily available blood test
- Should be performed under 3 circumstances
  1. To confirm diagnosis, if family history is unclear
  2. "At risk" or unaffected individuals
  3. At risk individuals wishing to conceive a child
     - "prenatal" or "pre-implantation" genetic testing
- Testing does NOT predict exact age of onset or severity of the disease progression
- Despite the availability of pre-symptomatic testing, only 5-10% of those at risk of inheriting HD choose to do so

Phillips et al. 2008

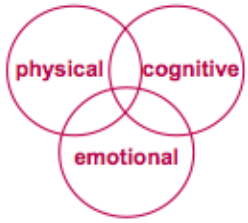
Genetic Counseling

- HD affects everyone in the family
- Counseling of "at risk" individuals is needed before proceeding with DNA testing
- Advice on the implications of a confirmed diagnosis
  - Impact on an individual's psychology, career, family planning decisions, relatives and relationships

Phillips et al. 2008

Clinical features of HD

- Movements
- Behavior/Psychiatric
- Cognition



HD – Movement disorder

- Chorea
  - Greek *choreia* – "dance"
  - Involuntary movements occur at rest and increases with distraction
  - Resolves during sleep
  - Typically starts in distal extremities (fingers, toes) and facial muscles
  - " Restlessness, fidgeting, twitching"
  - Individuals are often unaware of movements
- Motor impersistance
  - Inability to maintain an ongoing activity
  - Ex: Holding tongue out, maintaining grip ("milkmaid grip")
- Eye movement abnormalities

- Over time, movements progress to involve more proximal muscles (neck, trunk, arms/legs)
- Choreic movements become constant and interfere with walking
- Talking and swallowing become more problematic as the disease progresses
  - Choking, aspiration
- In late stages
  - Movements gradually change from HYPERkinetic to HYPOkintetic
    - Slow and rigid
    - Severe dysartira/anarthria
  - Gait instability and frequent falls

Roos et al. 2010

HD – Behavior & Psychiatric sx

- Behavior
  - Personality changes may be the earliest sign, often occur prior to onset of motor symptoms
    - Apathy
      - Diminished concern for things you used to care about
      - Lack of initiation of activities, conversations etc
    - Irritability, aggression
    - Rigid thinking
    - Impulsivity

Phillips et al. 2008

HD – Behavior & Psychiatric sx

- Psychiatric
  - Anxiety ~ 34-61%
  - Depression ~ 40%
    - Suicidality
      - 8 – 17 times more common than in general population
      - Risk highest at time of diagnosis and when sx interfere with independence
- Behavioral and psychiatric symptoms do not necessarily progress like motor symtpoms but rather fluctuate over time

Phillips et al. 2008

HD– Cognition dysfunction

- Subtle changes occur early, often before motor symptoms occur
  - "Executive dysfunction"
    - Poor planning & organization
    - Difficulty setting priorities, problem solving
    - Poor judgment
- As disease progresses, individuals with HD will develop "dementia"
- Impaired insight

Phillips et al. 2008

Not all dementia is Alzheimer's

- AD
  - Primary memory problem
  - Unable to learn and store new information
  - Unable to freely recall memory
- HD
  - Executive dysfunction
  - Slow to process but usually acurate
  - Slow to learn but able to do so
  - Free recall of memory slow but can answer with choices
    - Give cues

Phillips et al. 2008

Stages of HD

- Early
  - Chorea most prominent
  - Cognitive and behavioral sx affecting employment and relationships
  - Independent in ADL
- Middle
  - Obvious involuntary movements impairing walking
  - Speech and swallowing begin to be affected
  - Thinking and planning more impaired, no longer able to hold a job
  - Partial dependence
- Late
  - Severe movements now become more rigid → unable to walk or speak
  - Complete physical dependence → Nursing home or hospice care

Phillips et al. 2008

Treatment

- Mutidisciplinary Team Approach
  - Movement Disorders Neurologist
  - Psychiatrists
  - Nurses, social workers, dieticians
  - Therapists (PT/OT)
- Treatment aimed at treating symptoms to improve quality of life
  - Movements/Chorea
  - Cognitive dysfunction
  - Behavior/Psychiatric

Phillips et al. 2008

Pharmacologic treatment

TABLE 1. *Commonly used medications in the management of HD*

Drug	Mechanism of action	Indication	Side effects	Dosages
Tetrabenazine	Binds vesicular monamine transporters, inhibiting uptake of monoamines into synaptic vesicles; also blocks postsynaptic dopamine receptors	Hyperkinetic movement disorders	Drowsiness, Parkinsonism (around 30%), depression, insomnia, anxiety, acute dystonia, rarely confusion, orthostatic hypotension, hallucinations. NB No reports of tardive dyskinesia, but neuroleptic malignant syndrome has been reported.	12.5 mg bd, increased slowly to 12.5–25 mg tds (max 200 mg/day)
Risperidone	Serotonin-dopamine (D_2) antagonist	Hyperkinetic movement disorders; Mood swings; psychosis	Prolonged QT interval, postural hypotension, hyperglycaemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), fatigue, gastrointestinal	2 mg od, initially then usually 2–3 mg bd, max 16 mg/day. Liquid available
Olanzapine	Serotonin-dopamine (D_2) antagonist	Hyperkinetic movement disorders; Mood swings; psychosis; Depression; weight loss	Prolonged QT interval, postural hypotension, hyperglycaemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), marrow depression, hepatitis, fatigue. Caution with prostatic hypetrophy	10 mg od adjusted as required to 5–20 mg od. Max 20 mg/day
Citalopram	Selective serotonin reuptake inhibitor (SSRI)	Depression	Gastrointestinal, anorexia, hypersensitivity, drowsiness, syndrome of inappropriate antidiuresis (SIADH), postural hypotension, confusion	20 mg, increasing to 60 mg max
Fluoxetine	SSRI	Depression	Less sedating than citalopram, gastrointestinal, anorexia, hypersensitivity, SIADH, blood dyscrasia	20 mg, increasing to 60 mg max
Mirtazepine	Presynaptic α_2-antagonist, increases central noradrenaline and serotonin activity	Depression, weight loss	Drowsiness, tremor, myoclonus, reversible agranulocytosis	15 mg nocte, increasing to 45 mg (max) as required
Sodium valproate	Alters GABA, glutamatergic activity, and T-type calcium channel and potassium channel conductance	Mood swings	Hyperammonaemia, drowsiness, blood dyscrasia, hepatitis, dizziness, gastrointestinal, cognitive disturbance, endocrine	200 mg tds, increasing to 2.5g max if required
Carbamazepine	Inhibition of voltage-gated sodium channels. Action on monoamine, acetylcoline, and NMDA receptors	Mood swings, weight loss	Drowsiness, blood dyscrasia, hepatitis, hyponatraemia, dizziness, gastrointestinal	Usually 200–1,600 mg in 2–3 daily doses (max 2g)
Lamotrigine	Inhibition of voltage-gated sodium channels	Mood swings	Hypersensitivity, blood dyscrasia, dizziness, gastrointestinal, depression	25 mg/day increasing to 250 mg bd (max) if required

Phillips et al. 2008

Treatment - Movements

- Anti-dopaminergic therapy
  - Dopamine blockers (neuroleptics)
    - Typical antipsychotics
      - Ex: haloperidol, fluphenazine, thioridazine
      - Undesirable side effects
      - Potential to cause other movement disorders
    - "Atypical" antipsychotics
      - Ex: Risperidone, Olanzapine
  - Dopamine depleting drugs
    - Ex: tetrabenazine

Phillips et al. 2008

Tx – movements continued

- Atypical antipsychotics
  - Side effects:
    - Prolonged QT interval, postural hypotension, tardive dyskinesia, parkinsonism
- Tetrabenazine
  - Side effects
    - Drowsiness, depression, parkinsonism
- Other drugs
  - Remacemide
  - Riluzole
  - Amantadine

Phillips et al. 2008

Tx – Cognitive dysfunction

- Acetylcholinesterase inhibitors (Donepezil/Aricept)
  - Not beneficial in HD

Phillips et al. 2008

Tx – behavior / psychiatric sx

- Behavioral modification
- Pharmacologic therapy
  - Depression:
    - Mirtazapine, fluoxetine, citalopram
    - Mood stabilizers (carbamazepine, laotrigine, valproate)
    - ECT
  - Aggression
    - Citalopram, sertraline, propranolol, antipsychotics

Phillips et al. 2008

Nonpharmacologic treatment

- Tips for caregivers
  - Communication
  - Swallowing/Eating/Nutrition
  - Behavior
  - Bathing
  - Sleeping

Phillips et al. 2008

Communication

- Ability to organize thoughts and present them in an orderly way is compromised
- Speech may vary in volume, be interrupted by grunting sounds and hard to understand
- Patients can use non verbal communication like anger, withdrawal or short temper
- Tips: It is important to remember that although individuals with HD might not be able to speak, they may still understand you and what is going on around them
  - Be calm, gentle and matter-of-fact
  - Use short sentences
  - Ask questions with yes/no answers
  - Give choices (one or two)
  - Allow time

Nutrition & Swallowing

- Meal time can be difficult
  - People with HD often complain of constantly being hungry
    - Stuffing food in mouth
  - Difficulty coordinating movements needed to bite, chew and swallow
- Serious risk of aspiration
- Risk of malnutrition bc of increased energy expenditure
- Tips: Preventing weight loss
  - Patients often require bw 3500-5000 calories/day
  - Consider giving double and triple portions
  - Supplement meals with high calorie foods and drinks

Swallowing Problems “dysphagia”

- Tips: Reduce risk of aspiration
  - Minimize distractions
  - Sit up right during mean with chin tucked down
  - Remain upright for 30-45 minutes after the meal
  - Double swallow between bites
  - Thicker and colder liquids are better
  - Small bites and sips
- As swallowing becomes more impaired, may not get adequate nutrition by mouth
  - Feeding tube (PEG tube, G-tube) needs to be discussed

Behavioral Problems

- Tips: Remember that the patient is NOT deliberately trying to be difficult. The problem is occurring because of changes in his/her brain.
- Establish a routine
- Simplify the environment & remove distractions
- Limit number of activities to one at a time
- Keep number of people in a room at a minimum
- Avoid busy and noisy settings

Behavior – Apathy

- Tips: Do not mistake apathy for laziness
  - Remember, individuals with HD have difficulty initiating activities
  - Encourage participation

Bathing

- Many people with HD are reluctant to bathe in a tub or shower
- The individual with HD has to focus on maintaining balance, unfamiliar caregiver, modesty
- Tips:
- Keep shower time as short as possible
- Use a chair, hand held shower head, bath mits
- Minimize unfamiliar caregivers

Sleep Problems

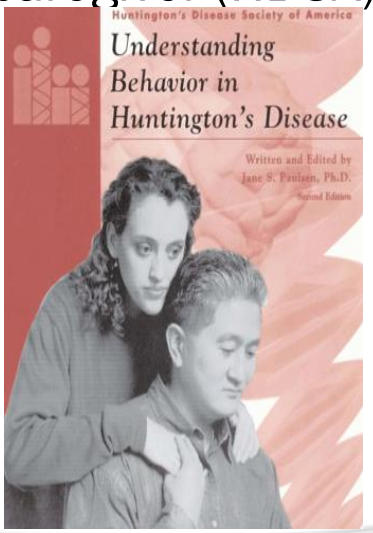
- Maintain a regular schedule
- Bedroom should be cool, quiet and dark at night, full of light during the daytime
- Avoid excessive napping in early evening

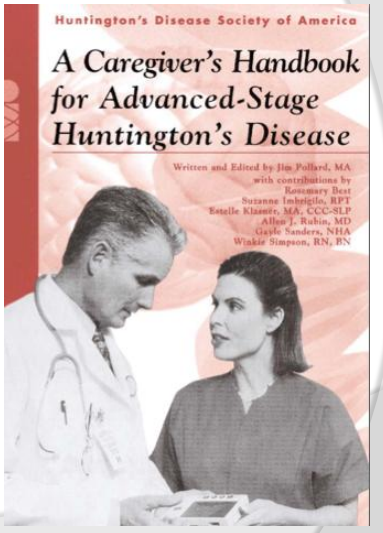
Summary - What can we do?

- People with HD are NOT intentionally trying to be difficult
  - Minimizing Distractions
    - Patients have difficulty organizing and prioritizing information
    - When they are over stimulated, may respond with frustration or anger
    - Very important during meal time
  - Safety
    - Task may become dangerous as the patient loses control over emotions, motor skills and judgment
    - Modify activity rather than completely restrict
  - Identity/Individuality
    - Surrounding patients by the things they most enjoy
    - Videos, pictures, pillows, blankets, books on tape

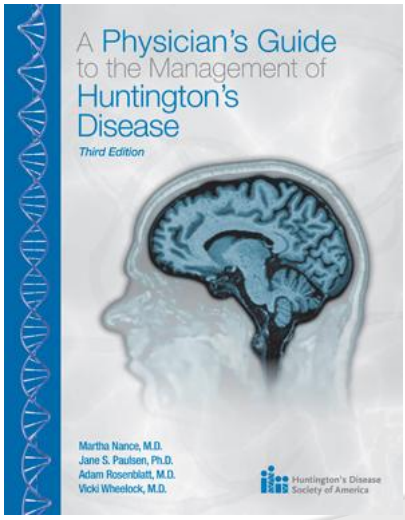
Resources

Resources – patients and caregiver (HDSA)





Resources – Physicians (HDSA)



HD clinical trials