Huntington’s Disease
Psychiatry

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--Many slides adapted from Adam Rosenblatt, MD
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Huntington’s Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespread degeneration

CAG-CAG-CAG (DNA)
↓
CAG-CAG-CAG (RNA)
↓
Gln---Gln---Gln (Protein)
(Q) (Q) (Q)
CAG Repeat length and Age of Onset of HD

- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—thus can roughly predict onset age
- Determinants of the rate of progression are still unknown

Quantification of Caudate Volumes: Regions of Interest

--Aylward et al Neurology 2004
White Matter Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- DTI: Water diffusion for fiber tract directionality
- Fractional anisotropy measure of white matter integrity
- SPM map of significant differences—blue and green represent HD Pre-Sx less than control

--Reading, Mori et al 2005
fMRI Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

• 7 Pre-Symptomatic HD
• 7 controls
• Stroop interference type task

• SPM subtractive analysis
  – Baseline from active (by group)
  – Pre-Sx from controls

Between-group differences of BOLD response with the “active” condition of the task

--Reading et al Ann Neurol 2004
Movement Disorder

- Involuntary movements - chorea
  - Begins with distal extremities
  - May also include vocal tics

- Impaired voluntary movements
  - Clumsiness, falls, swallowing, dysarthria
  - Eventually eclipses the chorea
  - Also “apraxia” difficulty organizing movements in space

- Sometimes treated with antidopaminergic drugs
  - Neuroleptics, benzodiazepines, reserpine/tetrabenazine
Dementia

• “Subcortical” dementia (vs Alzheimer’s disease)
  – Losses in speed, attention, and flexibility
  – Orientation, memory, language relatively preserved
  – May be more impaired than is obvious
• Impaired judgement is a big problem
  – Makes advance planning very important
Types of Psychiatric Disturbances

- Mood disorders
  - Depression and mania
- Obsessive-Compulsive symptoms
- Psychosis
- “Frontal” symptoms/ Personality change
  - Irritability, apathy, disinhibition
- Sexual disorders
- Delirium
Depression

• High prevalence
  – ~40% in HD by various estimates
  – Suicide rate 4-6x higher than normal
• Commonly underdiagnosed
  – Poor communication, atypical presentation
  – “Explained away” by clinicians
• Overdiagnosis is also a problem
  – Misinterpretation of symptoms, unnecessary meds
    • Differential includes apathy, abulia, akinesia, delirium, dementia
• Severity trumps other considerations
Treatment of Depression

• There is little evidence from research
  – Have used all classes of antidepressants with success
• Vulnerable to side effects
  – Sedation, falls, cognitive impairment
  – Similar to geriatric patients
• SSRI’s offer several advantages
  – May treat other “frontal” symptoms
• ECT effective and well tolerated
Mania

- Prevalence estimates for HD 4-10%
  - Small number of bipolar conditions
- HD “mania” may not be the usual type
  - Chronic disinhibition, irritability
- Conventional wisdom is not to use Lithium
  - Divalproex, carbamazepine, neuroleptics
Obsessive-Compulsive Symptoms

- Reported in HD and common in Tourette’s
- True OCD is relatively uncommon in HD
  - vs perseverative behavior
  - Also hoarding and other behaviors
- Both conditions may respond to medicine
  - Serotonergic antidepressants
  - Cognitive impairment limits psychotherapy
- Education of families is very important
Psychosis

• Prevalence in HD 3-12%
  – May result from a hyperdopaminergic state
• New onset prompts a search for causes
• Neuroleptics complicate movement disorder
  – Tend to favor “atypicals” for that reason
  – Tardive dyskinesia will be hard to spot
The “frontal” syndrome of HD

• “Frontal” is a pseudoanatomical term
• Name derives from similarity to other conditions
  – Often involving “subcortical” dementia
    • Parkinson’s disease
    • Fronto-temporal dementia
    • Traumatic brain injury
    • CVA
    • HIV
• Disorders of “executive” function
Personality Change or “Frontal” Behaviors

• “Frontal” disorders hard to define, characterize, treat
• Probably among the most common problems in HD
  – Rarely lead to a specific diagnosis
  – Significant cause of morbidity, institutionalization
• Often regarded as personality change
  – Apathetic
  – Irritable
  – Disinhibited
  – Impulsive
  – Obsessional
  – Perseverative
Apathy

• Emotional and cognitive aspects
  – Failure to initiate activities
  – Internal feeling of lack of interest
• Common in HD clinical practice
  – HD may be more apathetic than AD with similar cognition
  – Distressing to caregivers
• Large differential diagnosis
  – Mood, cognitive, Neurologic
• May not segregate with depression, aggression, irritability
Treatment of Apathy

• Is treatment necessary?
  – Often more distressing to caregivers than patient
  – Education and appropriate expectations
• Non-pharmacologic approaches
  – Schedule, stimulation, cueing, reinforcement
• Drug therapy
  – Stimulants: amphetamine, methylphenidate, pemoline
  – Non-sedating SSRI: fluoxetine, sertraline, citalopram
  – Dopaminergic: amantadine, selegilene, bromocriptine
Irritibility, Disinhibition, Perseveration

• May take the form of a personality change
  – Very distressing to caregivers
  – A cause of morbidity, institutionalization
  – Disinhibition and rigidity lead to explosions
• Behavioral management is vital
  – Place events in context
  – Identify and avoid precipitants
“Frontal” Pharmacotherapy

- Antidepressants
  - SSRI’s are among the most helpful
- Neuroleptics
  - Newer agents, if not needed for chorea
- “Mood stabilizers”
- Amphetamines
- Dopaminergic agents
- Others—amantadine, memantine
Sexual Disorders

- Most common problem is loss of libido
  - high prevalence in HD
- Some problems arise from disinhibition-rare
  - Voyeurism, paraphilias
- Situational problems
  - Changing relationships
- Antiandrogens may help truly hypersexual
Delirium

• Patients are extremely vulnerable
  – Loss of brain tissue
  – Susceptible to falls, dehydration, polypharmacy
• Delirium may mimic other psychiatric problems
  – Obtundation, arousal, lability, hallucinosis
• Nothing changes rapidly in HD
  – Always suspect delirium with new symptoms
  – IF FALL WITH HEAD INJURY CONSIDER SUBDURAL HEMATOMA
Conclusions

• HD is a neuropsychiatric condition
  – Amenable to rational treatment
• Obstacles must be overcome at every step
  – Difficulties in diagnosis, treatment, assessment
• Problems with attitude are often the worst
  – Do not regard these cases as hopeless
  – Do not regard depression as “normal”
• Many (?most) individuals with HD do just fine
HD Over the Lifetime

Neurobiological marker (arbitrary units)

Diagnostic (motor) threshold

Age

CAG < 30
CAG > 39 Untreated
Design of Therapeutic Trials for Pre-Symptomatic HD

Age

Neurobiological marker (arbitrary units)

CAG < 30  CAG > 39 Untreated  CAG > 39 Treated: hypothetical

Diagnostic (motor) threshold

Beginning of treatment