SLEEP DISORDERS IN HUNTINGTON’S DISEASE

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Pre-Talk Test

1. Which type of deficit emerges first in HD?
   A. Chorea  B. Cognitive  C. Sleep  D. Visual

2. Which area of the brain is most affected by HD?
   A. SCN   B. Cortex  C. Thalamus  D. Striatum

3. Expression of which gene peaks during the day?
   A. bax2   B. per2  C. bal1  D. NT1

4. Nocturnal melatonin release in HD is:
   A. Advanced  B. Delayed  C. Absent  D. Normal
Characteristics of HD

- Autosomal dominant disorder—IT15 region of the short arm of chromosome 4—expanded CAG region—abnormal huntingtin—aggregates
- Hypofunction and progressive loss of medium spiny neurons in the neostriatum
- Cognitive (primarily short-term memory loss), motor (choreic movements), and psychiatric symptoms (depression, anxiety, and compulsiveness)
Wisconsin Card Sorting Task

1. Red circle
2. Green star
3. Blue squares
4. Yellow crosses

5. Red crosses
"Then, as you can see, we give them some multiple choice tests."
Chromosome 4 Abnormality

- Region 4p implicated in bipolar disorder
- Marker D4S1582
- DRD5 gene (dopamine D5 receptor gene)
- Marker D4S2949

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## CAG Repeat Length and HD

<table>
<thead>
<tr>
<th>Allele</th>
<th>CAG Repeat Length</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td>Normal Allele</td>
<td>Less than or equal to 26</td>
<td>Normal</td>
</tr>
<tr>
<td>Mutable Normal Allele</td>
<td>27-35</td>
<td>Normal</td>
</tr>
<tr>
<td>HD allele with “reduced penetrance”</td>
<td>36-39</td>
<td>Normal/HD</td>
</tr>
<tr>
<td>HD Allele</td>
<td>Greater than or equal to 40</td>
<td>HD</td>
</tr>
</tbody>
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Age at onset by CAG repeat size
Developing treatments for HD

DNA: CAG repeat
Faulty huntingtin protein

Aggregates (or soluble protein)

Apoptosis
Impaired gene transcription
Impaired axonal transport
Impaired energy metabolism
Altered synaptic transmission
Excitotoxicity
Altered proteolysis
Oxidative stress

NERVE CELL DYSFUNCTION AND DEATH

SYMPTOMS
fMRI Studies in Presymptomatic HD

Control

Far HD

Close HD

Paulsen et al. 2005
Journal of Neuroradiology
HD Neuropathology

HD is a dominantly inherited, slowly progressive disease characterized by cognitive impairments, psychiatric disturbance and movement disorders. The striatum shows preferential degeneration.

HD brain and age-matched control brain
Photo from Marc Becher
Striatal Connections
Clinical Sleep Disorders in HD

- Wiegand et al. (1991) found disruption of nocturnal sleep in 16 inpatients with HD, including a disturbed sleep pattern with increased sleep onset latency, reduced sleep efficiency, frequent nocturnal awakenings, more time spent awake, an increased density of sleep spindles, and less slow wave sleep.

- These abnormalities correlated in part with duration of illness, severity of clinical symptoms, and degree of atrophy of the caudate nucleus.
Arousal versus Sleep

- Reticular formation contributes to cortical arousal and activation (pontomesencephalon)
- Locus Coeruleus contributes to arousal as its widespread norepinephrine releases correlate with exciting & novel events
- Basal forebrain contributes to arousal as its acetylcholine releases promote attention to time-associated perceptions
  - A smaller population release GABA into the cortex and serve to promote sleep
• Adenosine at adenosine receptors inhibits arousal and this effect can build up over time (sleep debt)

• Caffeine blocks adenosine receptors
Disrupted Circadian Rhythms in HD Patients and R6/2 Mice
The Suprachiasmatic Nucleus

- The optic chiasm is where the optic nerve crosses in the middle (nasal) area.
- Retino-hypothalamic pathway inhibits SCN.

- When light \textit{(zeitgeber)} fades, the unsuppressed SCN sends signals to the pineal gland to initiate melatonin production.
Resetting the SCN

- Special retinal ganglion cells that contain their own photopigment, slowly respond to changes in light levels that last
  - Active cells suppress activity of SCN
  - Inactive cells lead to SCN $\rightarrow \uparrow$ pineal gland production of melatonin (from tryptophan)

- Also
  - Brain halts production of histamine, norepinephrine, and serotonin
    - Associated with arousal
Melatonin and HD

- Morton et al. found that in R6/2 mice there was a marked disruption of expression of the clock genes *mPer2* and *mBal* in the suprachiasmatic nucleus, producing negative consequences for the production of melatonin and the circadian sleep rhythm.

- Alden et al. found dim light melatonin onset, defined as the time at which a salivary concentration of 4 pg/ml is reached (normally between 7:30 p.m. and 10:00 p.m.) was significantly delayed in 5 of 10 HD patients.
Per2 and BMAL1 Genes
Genetic Disruption of SCN in HD
Electroencephalogram

- Scalp surface electrodes measure averaged electrical activity (of cortex)
  - Amplified
- Correlated with eye movement by measuring muscle activity beside eyes
  - Polysomnograph
Sleep Stages

- **Alpha**: 8-12 Hz EEG, relaxation
- **Beta**: 13-30 Hz EEG, arousal
- **Theta**: 3.5-7.5 Hz EEG, intermittent during slow wave and REM sleep
- **Delta**: <4 Hz, during deep slow wave sleep
- **Sleep spindles**: 12-14 Hz, 2-5/min, maintaining sleep?
- **K Complex**: During stage 2, forerunner of Delta activity
• Several REM sleep cycles during a night’s sleep.

• Approximately 70% of newborn infant’s sleep is REM sleep. This declines to 30% by 6-months. REM sleep then declines to about 15% of adult sleep.
Orexin and HD

- Morton et al. found a dramatic atrophy and loss of orexin neurons in the lateral hypothalamus of R6/2 (HD) mice and in HD patients. Both the number of orexin neurons in the lateral hypothalamus and the levels of orexin in the cerebrospinal fluid were reduced by 72% in end-stage R6/2 mice.

- Alprazolam or chloral hydrate, two different sedative drugs, enabled R6/2 mice to develop regular sleep patterns and improved their cognitive function.
The Sleep “Flip-Flop” Mechanism

- Ventrolateral preoptic area of the hypothalamus promotes sleep. Activity increases when animals are kept awake.

- Adenosine buildup increases activity here.

![Diagram showing the sleep flip-flop mechanism](image)
Chorea and Sleep

- Some HD patients have restless sleep because of a large amount of involuntary movements at night.
- A small dose of fluphenazine, haloperidol (0.5-2 mg) or clonazepam (0.5-1 mg) at bedtime, may suppress the movements sufficiently to allow more restful sleep.
- Polysomnography or referral to a sleep disorder center may be helpful in these difficult cases.
Pharmacologic Treatments for Insomnia in HD Patients

- Should avoid benzodiazepine or barbiturate hypnotics because of the potential for tolerance, dependence, and delirium.

- Small dose of a sedating antidepressant such as trazodone (Desyrel), beginning at 25-50 mg and increasing to about 200 mg as necessary.

- Sedating tricyclics such as doxepin (Sinequan) or amitriptyline (Elavil) can be employed, but are highly dangerous in overdose.
Summary and Conclusions

- Although the most prevalent pathology in HD is in the striatum, it has global effects and can affect structures like the SCN which affects circadian rhythms and sleep cycles.

- There is new evidence implicating disruption of per2 and bal genes in the SCN, as well as loss of orexen cells in the hypothalamus in HD patients that are associated with sleep disturbances in HD.

- Pharmacologic treatments for sleep problems in HD patients are available, but possibilities of gene therapies may provide a more effective remedy in the future.
Post-Talk Test

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