Part 1
Parkinson’s Disease
Background:
Neuroanatomy of the motor system

Note: Given short time to the final the details of the anatomy will not be in the exam, but is important to know if one is to understand neuropathology of basal ganglia-related conditions such as Parkinson’s and Huntington’s
Subcortical Structures - Basal Ganglia
Parkinson's Disease (PD)

Neurodegenerative disorder

Usually after age ~50
  • Incidence rises with age
  • Affects 1-2% of population > age 65

Higher incidence in men (~60%) compared to women.
  • Reasons unclear (hormones vs lifestyle vs genetic factors)
Parkinson's Disease (PD)

Observed since ancient times

- Sanskrit Ayurvedic texts ~10th century BC refers to tremors, rigidity, drooling (Kampavata)
- Egyptian papyri and Bible references to tremors and drooling due to age
- Galen wrote an essay on “shaking palsy” that is thought to be a clear reference to PD (~150 AD)

James Parkinson: “An essay on the shaking palsy” (~1897, London)

Condition named by French neurologist Jean-Martin Charcot (~1865)
Parkinson's Disease (PD)

Symptoms

- Rigidity
- Tremor
- Akinesia/Bradykinesia
- Posture/Balance disturbances
- Cognitive deficits (esp. executive functions)
- Psychiatric/Mood symptoms
Parkinson's Disease (PD)

Genetic Basis:

Identical twins tend to develop around same age
Several genes identified

Environmental Factors:

Also known to affect PD but not all identified
Exposure to:
  Pesticides
  Metals
  Certain solvents
Traumatic brain injury
Not geographically uniform (diet? toxin exposure?)
Occupation (may be due to exposure to pesticides & other toxins)
A triad of motor symptoms

1. Tremor
   Most common first symptom, usually asymmetric and most evident in one hand with the arm at rest.

2. Rigidity
   Muscle tone increased in both flexor and extensor muscles providing a constant resistance to passive movements of the joints; stooped posture, anteroflexed head, and flexed knees and elbows.

3. Bradykinesia (slow movements)
   Difficulty with daily activities such as writing, shaving, using a knife and fork, and opening buttons; decreased blinking, masked facies, slowed chewing and swallowing.

Symptoms worsen as disease progresses.
Tremors

Usually first symptom

Often occurs in the hands or arms
Can occur in head, face, jaw, & leg
Often disappears during purposeful movement
Such as picking up an object
Tremors – Continued
Usually unilateral
Can become bilateral
Can worsen with stress
Postural manifestations

- Postural instability
- Rigidity
- Stooping

Postural changes can cause balance instability
<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Two</td>
<td>Bilateral</td>
</tr>
<tr>
<td></td>
<td>No balance impairment</td>
</tr>
<tr>
<td>Three</td>
<td>Balance impairment</td>
</tr>
<tr>
<td></td>
<td>Mild to moderate disease</td>
</tr>
<tr>
<td></td>
<td>Physically independent</td>
</tr>
<tr>
<td>Four</td>
<td>Severe disability</td>
</tr>
<tr>
<td></td>
<td>Still able to walk &amp; stand unassisted</td>
</tr>
<tr>
<td>Five</td>
<td>Wheelchair-bound or bedridden unless assisted</td>
</tr>
</tbody>
</table>
Patients also suffer from non-motor symptoms

Olfactory changes
GI dysfunction
Sleep disturbances

**Depression:** Mild to moderate depression \(\sim 50\%\) of patients.

**Cognitive impairment:** Mild cognitive decline including impaired visual-spatial perception and attention, slowness in execution of motor tasks, and impaired concentration in most patients; at least \(1/3\) become demented during the course of the disease.
Other Correlates

Some studies report changes in neural oscillations (e.g., theta and beta bands)

Lewy body protein deposits may be found (Lewy body dementia can be confused with Alzheimers and Parkinsons)
Parkinson’s Disease

Cut section of the midbrain where a portion of the substantia nigra is visible

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease
**Dopaminergic system**
(dopamine):

**Nigrostriatal pathways** (orange projections)
- Active in maintaining normal motor behavior
- Loss of DA is related to muscle rigidity and dyskinesia in Parkinson's disease

**Mesolimbic pathways** (purple projections)
- Dopamine release causes feelings of reward and pleasure
- Thought to be the neurotransmitter system most affected by addictive drugs
- Increases in DA activity may be related to schizophrenia
Reduced dopamine in Striatum
Excessive activity in STN, GPi
Vitek, 2008
Loss of dopaminergic neurons linked to symptoms
Symptoms can take years to become visible
Treatment

Why not give dopamine? Not quite...

- Dopamine itself, does not pass the blood-brain barrier
- **Levodopa (L-dopa)** can be given to pass into the brain and the nerve cells then use it to make dopamine
- Efficacy tends to decrease as the disease progresses.
- Chronic treatment associated with adverse events (motor fluctuations, dyskinesias and neuropsychiatric problems). Cf schizophrenia lecture

Other medications

- Dopamine-agonists: act on dopamine receptors, mimic natural dopamine, not as effective as L-dopa
- Anticholinergic drugs: can help relieve tremor in mild to moderate disease
Treatment: Deep Brain Stimulation

Look away if squeamish
DBS surgery
Localization of the subthalamic nucleus (STN)
DBS of STN

Can be life-changing for some patients

Motor functions are often addressed successfully

However, effects on cognitive and affective symptoms not as clear

- Can even have adverse effects
- For more see Vitek, 2008
Part 2
Huntington’s Disease
What is Huntington’s Disease

- First described by Dr George Sumner Huntington of Long Island in 1872 in ‘Medical and Surgical Reporter’
- ‘One of the most remarkable papers in the history of medicine’
- All the cardinal features of HD were recognized:
  - Adult onset
  - Progressive course
  - Choreic movements
  - Intellectual impairment
  - Psychiatric disturbance
  - Hereditary nature
Symptoms and genetic basis

• **Autosomal**, dominantly inherited, neurodegenerative disorder characterized by ‘triad’ of cognitive, affective and motor disturbance

• 5-10 cases per 100 000
• Affects **all** ethnic groups
• Gene cloned in 1993
• Mutant Huntingtin protein (expanded CAG repeats)
• **Genetic test** available
• Only ~4% of ‘at risk’ individuals choose testing
• Raises very complex and fascinating ethical issues
How does mutant Huntingtin destroy cells?

• Still not clear
• Huntingtin expressed in all cells
• Massive effort underway in cell biology
• Aided by good transgenic mouse models

Note: huntingtin is a protein. The gene coding for huntingtin is IT15 ("interesting transcript 15") gene
Finding the HD gene

Mapping Fate

A Memoir of Family, Risk, and Genetic Research

With a New Afterword

Alice Wexler
Living with the burden of family HD? Would you want to know?
CAG repeats and age of onset

• < 36 CAG repeats for healthy people

• > 37 or more repeats (up to 121) will develop HD

• Number of repeats roughly predicts age of neurological diagnosis

• But other symptoms begin long before motor problems …
Early Onset Huntington’s

About 6% of cases start before the age of 21
Akinetic-rigid syndrome
Faster progression
Called juvenile, akinetic-rigid or Westphal variant HD.
Motor and other symptoms

• **Choreic** movements
  - classic HD symptom
  - involuntary ‘writhing’
  - saccade system
  - early finger tapping problems

• Psychiatric/affective symptoms
  - impulsivity/irritability/aggression
  - suicidality and depression
  - disgust recognition impairment

• Cognitive impairments
  - Executive function
  - Visual recognition memory
  - Feedback-driven learning and control
Drugs for Treatment

No cure but symptoms can be addressed:

Physical and occupational therapy

Drugs

Some antipsychotics and benzodiazepines may be used for chorea
Parkinsonian drugs for the juvenile variant with rigidity
Psychiatric drugs for mood and behavioral symptoms
Choreic movements:
http://www.youtube.com/watch?v=kINXljs_V3M

Virginia Pilot piece on HD:
http://www.youtube.com/watch?v=HBLrY_nXU_U
Neuropathology in HD

- Classically seen as a basal ganglia disorder
- Striatal GABAergic medium spiny cells cells take a massive hit, but, still not known where/how HD begins
- Cortical functional change and atrophy evident long before manifest neurological signs (‘onset’)
- Classic view is changing - this is not just a basal ganglia disorder, even in the earliest change
- Mouse studies show functional change (physiological) in cortico-striatal projection neurons even before striatal cell death
Longitudinal structural imaging of caudate in premanifest HD

- Caudate volume reduced even 20 years away from onset
- Rate of cell loss accelerates ~11 years from onset
- At time of onset, ~50% of striatal cells gone

Aylward et al 2004, Neurology