Phenomenology

1. Hypo/bradykinetic (Parkinsonism)
2. Hyperkinetic
   • Tremor - rhythmic: rest, postural, or kinetic
   • Dyskinesias - choreiform or dystonic
     Especially the tongue if tardive dyskinesias
     Chorea - brief, jerky, espec hands/feet
     Dystonia - more sustained, may be fixed, co-contractions
   • Athetosis - slow, writhing, continuous, especially distal
   • Ballism - proximal rapid, flailing movements (STN)
   • Myoclonus - rapid, isolated jerks - cortical or spinal
   • Tics - premonition
   • Stereotypy - repetitive, stereotyped

Phenomenology (cont.)

3. Ataxia (Cerebellar)
   wide based gait, dysmetria, nystagmus, scanning speech

Parkinson’s

Idiopathic Parkinson’s disease (PD)
Multiple System Atrophy (MSA)
  Striatal-Nigral Degeneration, Olivo-ponto Cerebellar Atrophy, Shy-Drager
Progressive Supranuclear Palsy (PSP)
Vascular Parkinson’s (Binzwanger’s Dementia)
Normal Pressure Hydrocephalus (NPH)
Cortico-basal Ganglionic Degeneration (CBGD)
Lewy Body Disease (LBD)
Drug-induced Parkinson’s
  neuroleptica, metoclopramide

Essential Tremor

• ~0.4 - 3.9% prevalence, 1.3 - 5.1% above age 60; often misdiagnosed as PD
• Autosomal dominant inheritance, idiopathic
• Pathophysiology: thought to originate from abnormal cerebellar signaling, possibly involving the inferior olive in the brainstem.
• Clinical: postural/kinetic (action) tremor, can be asymmetric, lacks additional features, suppressed by ETOH.
• Tx: beta-blockers, primidone, topiramate, VIM DBS
Essential Tremor video

Tardive Dyskinesia
• Iatrogenic (preventable), exposure to neuroleptics, metoclopropamide (Reglan): risk highest in elderly in whom risk 25-30%
• clozapine and quetiapine not definitively proven to cause in those without prior exposure to other agents; risks of most other newer agents not adequately proven to be better than traditional neuroleptics, especially at higher doses (i.e., dose dependent risk for most agents).

Tardive Dyskinesia (cont.)
• Tx: occasional remission upon discontinuing, often worsens
  – DA depleting agents: reserpine, tetrabenazine (also, DA-blocker)
  – switching to quetiapine, clozapine or other atypical at lowest dose might be beneficial or necessary
  – GPI DBS may be effective

Huntington's Disease
• Prevalence ~4-5/ million, autosomal dominant, essentially 100% penetrance
• Increase in CAG repeats on Chrom 4 (nl <35-40), results in an elongated N-terminal polyglutamine expansion in the huntington protein; leads to striatal, other neuronal dysfunction and death.

Huntington's Disease (cont.)
• Clinical:
  – variable age of onset correlating with # of CAG repeats, most commonly 4th-5th decades, rarely in childhood; genetic anticipation, particularly with paternal transmission
  – progressive choreathetosis; Westfall variant in young-onset
  – often early personality change with progressive dementia and eventually psychosis
  – progressively debilitating with death generally within 10-20 yrs, more rapid with younger onset.
  – Differential: TD, stroke, Sydenham’s, Neuroacanthocytosis
• Tx: neuroleptics effective for chorea, pychosis (rarely DBS)

Dystonia
• Defined physiologically by co-contractions of antagonist muscles
• Clinical Classification
  1. Primary Dystonias- pure dystonias, in adults: most commonly idiopathic and focal, including torticollis; younger onset generalized forms, including DYT1 Dystonia (idiopathic torsion dystonia)
  2. Dystonia-Plus Syndromes- include Dopa-responsive dystonia- GCH1 (DYT5) or TH deficiency, Myoclonic dystonia (DYT11)
  3. Heredodegenerative Dystonias- PD, Wilson’s Disease, others
  4. Secondary Dystonias- Stroke, encephalitis, trauma, drugs, others
  5. Paroxysmal Dyskinesias- freq autosomal dominant (DYT8, DYT10)
Dystonia (cont.)

- Tx:
  - L-dopa trial (DRD)
  - anticholinergics, anti-spasmodics, clonazepam—limited benefit
  - Botox highly effective for focal
  - Baclofen pump, *GPI DBS

Tourette’s Syndrome

- Prevalence ~1% in juveniles (~10% for tics), males > females, a genetic disorder, possibly autosomal dominant inheritance
- Clinical:
  - Criteria: onset before age 18, multiple motor & ≥ 1 vocal tics
  - Motor tics usually begin between ages 3-8 with facial tics (eye blinking); phonic tics (sniffing, throat clearing) typically follow motor tics by several yrs
  - Tics occur in bouts with weekly and monthly fluctuations
  - usually peaks around age 10; typically symptoms improve by age ~18 (mostly disappearing in ½). In extreme forms self-injurious hitting or biting and coprolalia
  - OCD, ADHD, depression

- Tx:
  - Behavioral therapy
  - α2 adrenergic agonists (guanfacine, clonidine)
in milder
  - Neuroleptics
  - Tx of additional features

Restless Leg Syndrome

- Probable autosomal dominant in a majority; prevalence ~10-12% among adults, approaching 20% in those ≥80 years old.
- Four obligatory criteria: 1) urge to move the legs, 2) worsening with rest, 3) relief with activity, 4) intensification during the evening
- Discontinue SSRIs, MAO’s, lithium, antihistamines, neuroleptics check morning fasting serum ferritin, B12, folate

- Tx:
  - Fe supplementation for ferritin < 50 µg/L (low normal range).
  - Counsel to avoid prolonged idleness and sleep deprivation
  - DA agonists first-line even in elderly (levodopa probably carries an especially higher risk of augmentation—though no controlled study)
  - Gabapentin (neurontin) mainly be beneficial if painful symptoms
  - Opiates frequently beneficial and addiction rarely an issue
Wilson’s Disease

• Prevalence ~1-2/100,000, autosomal recessive
• Large # defects on Chrom 13 coding for a copper-binding ATPase, leads to reduced ceruloplasmin binding of Cu, reduced biliary excretion, and pathological deposition of Cu.

Wilson’s Disease (cont.)

• Clinical:
  – Onset usually 2nd, less often 3rd decade, reports as late as mid-50’s.
  – Liver failure; initially may be only elevated liver enzymes.
  – Wing-beating tremor, parkinsonism, dystonia (fixed grimace), chorea.
  – Emotional lability, cognitive decline, psychosis may occur.
  – Kayser-Fleischer rings at margin of cornea in most all with neurological

Wilson’s Disease (cont.)

• Dx:
  – Slit lamp, reduced serum ceruloplasmin/Cu, elevated urine Cu; liver bx
  – Genetic testing- impractical in most cases due to large # mutations

• Tx (highly responsive): 
  – Dietary Cu restriction, Cu chelating agents; liver transplant curative
  – *Screening of relatives

Cerebellar Syndromes

• Alcoholism- wide-based gait, superior-anterior vermal atrophy
  – Wernicke’s encephalopathy- triad: acute mental confusion, ataxia and ophthalmoplegia- thiamine deficiency

• Paraneoplastic Syndrome- anti-purkinge cell antibodies; typically subacute (i.e., fairly rapid) progression, can present mostly unilateral; tx of underlying cancer can improve or arrest, ?IVIg for early

• Drugs, small or larger vessel strokes, primary cerebellar degeneration, MSA, NPH

Cerebellar Syndromes (cont.)

• Spinal Cerebellar Ataxias- mostly autosomal dominant (triple repeats in a majority)- testing readily available for most as a panel
  – ?14 SCA’s identified to date
  – Often pyramidal involvement, anterior horn cell loss, neuropathy
  – SCA3,6- most common
  – SCA1-2 (and 3)- oculomotor defects
  – SCA3 (Machado-Joseph)- dystonic, other extrapyramidal features:
    – Av. onset- mid-late 30’s
  – SCA6- pure cerebellar, onset typically 60’s, incr nystagmus with hyperventilation