Huntington's disease

Definition
Progressive autosomal dominant movement, cognitive and psychiatric disorder

Epidemiology
Rare – 2.7/100,000 K. Enriched in founder populations.

Genetics
Huntingtin gene
trinucleotide repeat (CAG, polyglutamine)
chromosome 4p
AD inheritance
Full penetrance at repeat >38
Expansion over generations, particularly paternal inheritance -> clinical “anticipation” (earlier & more severe phenotype)
no apparent family history in up to 8 percent of patients with genetically proven HD

Pathophysiology
Huntingtin protein
large protein in all cells
insoluble when purified
Knock-out is embryonic lethal, rescued by mutant huntingtin
CAG repeats -> polyglutamine (“polyQ”)
Reportedly a study that CAACAG… = poly Q less pathogenic than CAGCAG… (REF: Li. RNA toxicity is a component of ataxin-3 degeneration in Drosophila. Nature 2008;453 (7198): 1107–1111. doi:10.1038/nature06909. PMID 18449188.)

Pathology
Severe caudate>putamen (striatum) atrophy, especially of medium spiny neurons
Loss of neurons, increase in glia
Loss of processes, aberrant growth
Also global atrophy
Nuclear inclusions reactive for huntingtin 10-20% at most depending on brain region, some cytoplasmic or punctuate staining as well

Clinical Features
(REF: http://www.uptodate.com/contents/image?imageKey=NEURO%2F15461&topicKey=NEURO%2F4907&rank=38-150&source=see_link&search=dementia)

Neurologic
Chorea
Dystonia
Eye movement slowing
Hyperreflexia
Gait abnormality
Myoclonus (rare)
Parkinsonism (late stages)
Psychiatric
Apathy
Irritability
Depression
Delusions
Aggression
Anxiety
Disinhibition
Paranoia

Cognitive
Poor judgment
Inflexibility of thought
Loss of insight
Decreased concentration
Memory loss
Subcortical dementia

Radiology
Flat ventricles sides, no bulge of caudate
Putamen decreased (not necessarily larger than GP, which it usually is)
Changes may start 10-15y before symptoms
Pathologic changes may start in corticostrial axons (REF: Sapp. 1999?)

Management
No neuroprotective treatments

Chorea
DA modifying: Tetrabenazine (TBZ): up to 100 mg/d. Side fx: depression/suicidality, parkinsonism.
Neuroleptic agents may be used, but limited support
Glut modifying: Amantadine (300–400 mg/d) or riluzole (200 mg/d). Side fx: elevated LFTs w/riluzole
Modest: nabilone


Experimental therapy approaches
Silence gene (w/other nucleic acids?)
Promote clearance
Target dysfunction at presymptomatic stage