CASE 9: FAMILY HISTORY OF HUNTINGTON'S DISEASE (Slide CC-1)

1. In HD there is progressive atrophy of the caudate nucleus and, to a lesser extent, of the putamen. As the disease progresses, diffuse cortical atrophy occurs as well. The cause of the neuronal cell loss is not known but may involve some form of excitotoxicity.

2. GABAergic and enkephalinergic neurons of the striatum projecting to the external segment of the globus pallidus (indirect pathway) are more severely affected in HD, particularly early on. The loss of inhibition of neurons in the external segment of the globus pallidus causes them to fire more frequently and to, therefore, inhibit the subthalamic nucleus. This results in loss of excitatory drive to the internal segment of the globus pallidus / substantia nigra pars reticulata. The net result is decreased activity in the inhibitory output pathways of the basal ganglia. Disinhibition of the ventral lateral nucleus of the thalamus in this manner is thought to account for the hyperkinetic movements seen in HD.

3. HD is a tragic illness which usually presents in the second through fifth decade. Progressive degeneration of the striatum results in the characteristic generalized choreaform movements which become gradually more severe with time. Typically, the movements are exaggerated by walking and do not occur during sleep. Other manifestations of this hyperkinetic state may include diminished tone, "hung up" reflexes (e.g. the knee will not immediately fall back down after a patellar tap), and motor impersistence (i.e. -tendency to sustain hand grip or other task only briefly). Degeneration of the striatum along with cortical atrophy are though to account for the emotional and intellectual changes seen in this disorder as well as for the abnormal saccadic eye movements.

The initial presentation of this illness can be subtle and quite variable. In some cases isolated motor or emotional symptoms may precede other manifestations by several years. Understandably, individuals at risk often go through alot of emotional stress regardless of whether they ultimately develop the disease, sometimes making initial diagnosis difficult. HD produces a long agonizing decline, ultimately, leading to death after ten to twenty years due to complete motor and intellectual incapacitation usually by aspiration pneumonia or other overwhelming infection.

Our patient is in the most common age range to begin to develop symptoms. He has some involuntary movements, and his history suggests a decline in interpersonal relations as well. He seems to deny his symptoms strongly, and at this stage some of the features of his history and physical exam are typical while others are not. Most important, however, is his family history (see also below) which together with his presentation make the likelihood of early HD high.

4. Dopaminergic projections from the substantia nigra pars compacta are thought to inhibit striatal neurons of the indirect pathway and to excite neurons of the direct pathway. In either case, diminished dopaminergic transmission should result in an overall decrease in activity in the ventrolateral nucleus of the thalamus and a decrease in the involuntary movements of HD. Agents acting both presynaptically (e.g. reserpine) and postsynaptically (e.g. haloperidol) have, therefore, been tried with modest success. Cholinergic neurons in the striatum are thought to cause excitation, preferentially of neurons projecting to the external segment of the globus pallidus (indirect pathway). Therefore, cholinergic agonists can diminish symptoms of HD. Note that for both the dopaminergic and cholinergic systems, drugs that improve HD will worsen Parkinson's disease and vice versa. Another class of drugs used in treatment of HD is the GABA analog baclofen. It's mechanism of action is less clear but may involve inhibitory actions in the basal ganglia as well as in other areas of the CNS including the spinal cord. Overall, the

medications available today for HD disease provide only a moderate improvement in symptoms and do nothing to slow the progression of the disease.

5. HD is inherited as an autosomal dominant trait with complete penetrance. Children of individuals with HD, therefore, have a 50% chance of carrying the gene and developing the disease.

Clinical Course:

Based on his clinical presentation and family history a diagnosis of early Huntington's disease was made in our patient. He was referred to a neurologist and as his symptoms increased he was started on baclofen, which had a modest effect in decreasing his involuntary movements.

Three years later his symptoms had progressed substantially, and he was admitted to the hospital for further evaluation. In the interim he had lost his job as a salesman because "business was slow" and was recently fired as a newspaper distributor because "I was robbed". In addition, he was recently divorced. Exam: Normal mental status except for mild irritability, and speech which had some repetition errors with nonsense syllables, and was slightly garbled at high speeds. He had developed paroxysmal involuntary twitches of all four limbs distally. Gait - slight waddling with some dystonic arm carriage. Head CT was normal except for very slight enlargement of lateral ventricles. EEG-low voltage, otherwise normal.

Eleven years after initial presentation the patient was readmitted after expressing suicidal thoughts when his driver's license was revoked. He was apparently stopped by the police while "trying to make left turn;" unable to say why.
He had last worked about one year previously doing part time paper deliveries. He was still able to live independently at home. Exam: Mental status - A&Ox3, fluent, but with abnormal rhythm of speech, follows complex commands, memory and calculating skills intact, labile affect, frustrated, angry and impulsive - e.g., threatens suicide if can't drive, poor insight into illness, denies any abnormalities in speech or movements, feels dependent on car, fears loss of independence, denies symptoms of major depression. Motor exam was notable for hyptonia, motor impersistence, and choreaform writhing movements of the tongue , arms, neck, and torso. The involuntary movements were worsened by gait, and he was unable to tandem (heel-toe) walk. An MRI of the head was done as discussed below.

MRI:

T1 weighted coronal images at the level of the optic chiasm are shown for a normal individual (left image) and for our patient (right image). In both images identify the following structures: the frontal lobes, the insula, the temporal lobes, the sphenoid sinus, the intracavernous portion of the carotid arteries just inferolateral to the optic chiasm, the cingulate gyrus, the corpus callosum, the septum pellucidum and the lateral ventricles (which portion of the lateral ventricles is shown at this level?). Note that in the normal individual (left), the head of the caudate nucleus forms a prominent gray matter bulge in the lateral aspect of the lateral ventricles. The anterior limb of the internal capsule and the putamen can be seen as well. In contrast, the caudate and putamen in our patient (right) are so atrophied that they are not even distinguishable from the white matter. The lateral aspect of the lateral ventricles are flattened or even slightly concave. Note that there is diffuse cortical atrophy in our patient as well.

Epilogue:

The patient was treated with dopamine antagonists such as haloperidol with little benefit. He was discharged home once it was ascertained that he was no longer suicidal and followed by

both a psychiatrist and a neurologist as an outpatient. Within two years he could no longer be managed at home and required admission to a chronic inpatient psychiatric facility where he remains to the present time.