

Huntington's Disease

Pinky Agarwal, M.D. and Lauren C. Seeberger, M.D.

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by abnormal movements manifested as chorea, bradykinesia and dystonia. There are also cognitive abnormalities characterized by disorders of attention and obsessive thoughts. The mutation is an expansion of a trinucleotide repeat in a gene on chromosome 4. This article outlines current treatment options.

Introduction. Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by abnormal movements manifested as chorea, bradykinesia and dystonia. There are also cognitive abnormalities characterized by disorders of attention and obsessive thoughts. The mutation is an expansion of a trinucleotide repeat in a gene on chromosome 4.

Clinical Manifestations. Huntington's disease is a fully penetrant, autosomal dominantly inherited, progressive neurodegenerative disease that causes disorders of motor control, emotional control, cognitive ability, and involuntary movements, classically choreic. The mean age of onset is approximately 40 years.

Several signs may portend onset of clinically manifest Huntington's disease: increased motor restlessness, slowing of saccadic eye movements, and slowing or dysrhythmic production of rapid, repetitive movements of the fingers or tongue. A number of individuals have prominent mood, thought, or personality disorders that present in the years prior to onset of definitive motor signs. Cognitive changes may also precede onset of motor definitive

symptoms. In the earliest stages of Huntington's disease, disturbances of problem-solving abilities, memory deficits, visuospatial skills, and attention disorders often lead to a decline in performance at work or in the home.¹

Because of its serious implications, the diagnosis of manifest Huntington's disease is reserved for at-risk persons who have developed chorea or another movement disorder. Juvenile cases (less than 20 years of age at onset) constitute about 5.4 percent of all cases of Huntington's disease.² Juvenile cases and occasional young adult cases can present with prominent parkinsonism or rigidity-dystonia with little or no chorea.

Motor Disorder. Chorea, from the Greek meaning "to dance," is an involuntary movement around multiple joints. Huntington's disease displays generalized choreiform movements. The mouth, trunk, and proximal as well as distal muscles are prominently affected. More flowing and somewhat slower choreoathetotic movements also often occur with more advanced disease as do fast, large amplitude, flinging movements resembling ballism.

Huntington's disease is a disorder of



Dr. Agarwal did her neurology training at NJ Neuroscience Institute. She did fellowship in movement disorders at Columbia University, NY. She has been practicing subspecialty movement disorders at the Colorado Neurological Institute since 2003. Her special areas of interest are Parkinson's disease and parkinsonism, tremor, dystonia including botulinum toxin injections, restless leg syndrome and tics/tourette's syndrome.



Dr. Seeberger earned her undergraduate degree from Vanderbilt University and received her MD from the University of Alabama. Her fellowship training is in movement disorders at UMDNJ - Robert Wood Johnson Medical School and she is Board Certified in neurology. Dr. Seeberger has written and lectured extensively on movement disorder and is currently involved in CNI research projects to develop treatments for Huntington's disease and Parkinson's disease.

voluntary motor control that causes progressive physical disability. There is a serious impairment in sequential movement. Mimical apraxia is common although language skills remain mostly intact. Patients are unable to learn complicated motor skills.

Other motor signs include bradykinesia, dystonia, imbalance, and speech disturbances. Bradykinesia generally coexists with chorea in the adult form of illness. A parkinsonian state with marked slowing of eye movements is seen in the juvenile onset cases (Westphal variant); seizures and myoclonus commonly complicate the course of juvenile onset Huntington's disease. Deep tendon reflexes are hyperactive in Huntington's disease. Poor balance manifests in mid to late stages of disease for both adult and juvenile forms with frequent falling and eventual wheelchair or bed-bound state. On examination, broad based stance and gait are common, and tandem walking is often impaired. Speech and swallowing dysfunction develop midstage of the illness and ultimately lead to inability to communicate and swallow. The movement disorder in adult onset Huntington's disease changes with time.

Chorea tends to slow and may be replaced by dystonia-rigidity in the end stages. Careful reviews of medications should be undertaken as the clinical picture changes to ensure that neuroleptic or other drug use is not contributing to motor dysfunction.

Psychiatric Disorder. Psychiatric disorders are prevalent in patients with Huntington's disease; including psychosis with rare visual hallucinations, a delusional thought disorder, mood lability, anxiety, irritability, mania, obsessive behavior, or rigidity of thought. Disabling or over-

whelming apathy from frontal lobe dysfunction is not unusual. Depression is the most common psychiatric manifestation of Huntington's disease and may be accompanied by emotional irritability with outbursts of disruptive behavior. Suicide occurs in 5 percent to 10 percent of Huntington's disease patients, and there is an increased risk of suicide for those at-risk for the disease.³ Frank psychosis is relatively unusual, though delusions may occur. Obsessive ideation is common and may respond to SSRIs.

Cognitive decline occurs in all patients and may be more, less, or equally as disabling as the motor disorder in different patients¹. Patients tend to be disorganized and suffer from lack of initiative. Some may show no awareness of their movement or cognitive disorder. There is usually a more rapid decline in visuospatial as compared to verbal skills. Also, a more dramatic drop in performance IQ as opposed to verbal IQ scores is seen⁴.

Etiology. Huntington's disease results from an expanded and unstable trinucleotide repeat in the IT15 gene on the short arm of chromosome 4. There is a 50 percent chance of inheriting the gene from an affected parent. The gene produces a protein called huntingtin. Three nucleotides, cytosine-adenine-guanine, form a trinucleotide and are repeated over and over in this gene normally. A person may have as many as 35 repetitions of the CAG trinucleotide in the Huntington's disease gene. Persons with more than 39 repeats will develop Huntington's disease, and those with 36 to 39 repeats are "indeterminate" and may or may not develop the disease. Such indeterminate individuals may have offspring with clinical Huntington's disease who have a more

expanded CAG repeat length in the gene.⁶

Epidemiology. The prevalence of affected individuals in the United States is estimated at 5 to 10 per 100,000.⁷ Approximately 2 to 4 times as many individuals have inherited the mutation but are as yet asymptomatic.

Diagnostic Workup. The diagnosis can be made on the basis of the clinical presentation described above in the context of a confirmed family history of Huntington's disease. MRI and CT scans show prominent caudate atrophy in young patients with moderate disability but may be within the normal range of patients with early signs of Huntington's disease. DNA diagnostic testing can now determine whether a patient with a suspicious clinical syndrome has Huntington's disease and is invaluable in clarifying uncertain situations. Appropriate genetic counseling should be available. Neuropsychological testing can be helpful in delineating the patient's degree of cognitive disability.

Prognosis and Complications. Huntington's disease is a progressive neurodegeneration that leads to death via medical complications. Complications during the course of illness include speech and swallowing problems, imbalance, incoordination, and falling, as well as impaired judgment and cognition. Death usually is caused by infectious complications of immobility in the late stages of the illness.

Management. Treatment of patients with Huntington's disease requires a coordinated effort on the part of a medical, psychiatric, social service and physical therapy team. For those who are gene

positive and asymptomatic or early symptomatic, focus should be on treatments that may potentially slow disease progression. A national trial showed neither remacemide nor coenzyme Q10 given alone or in combination has any significant effect on progressive functional decline. Minocycline study in delaying disease progression, showed that it was well tolerated and had no serious adverse events.⁸

A 1-year placebo-controlled clinical trial of creatine supplementation (5mg/day) in Huntington's disease did not improve functional, neuromuscular, or cognitive status in patients with early disease.⁹

Depression often responds partially to treatment with standard antidepressants. Carbamazepine or valproate may improve patients with a manic disorder. Delusions and paranoia often respond to low dose neuroleptics. Carbamazepine, SSRIs, clonazepam, propranolol, valproate, and clomipramine are just some of the medications that may be helpful for irritability and emotional dyscontrol. Risperidone may be useful for management of psychiatric disorders in patients with Huntington's disease.

Chorea in Huntington's disease may be treated effectively with neuroleptics. Other agents used include tetrabenazine, benzodiazepines, and propranolol. In a randomized trial, amantadine hydrochloride treatment at doses of 300mg/day had no effect on Huntington's chorea, although most patients felt subjectively better.¹⁰

In a multicenter placebo-controlled trial, riluzole 200mg/day decreased the intensity of chorea without improving functional capacity. It caused reversible liver transaminase abnormalities that require long-term monitoring.¹¹ Dystonia and rigidity may complicate end stage disease and can be treated with local injections of

1. White FR, Vasterling JJ, Koroshetz WJ, Myers R. Neuropsychology of Huntington's disease. In: White R, editor. *Clinical syndromes in adult neuropsychology; the practitioner's handbook*. Amsterdam: Elsevier, 1992:213-248.
2. Nance MA. Genetic testing of children at risk for Huntington's disease. *Neurology*. 1997;49:1048-1053.
3. Sorensen S, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. *J Med Genetics*. 1992;29:911-914.
4. Zakzanis KK. The subcortical dementia of Huntington's disease. *J Clin Exp Neuropsychol*. 1998;20:565-578.
5. Rubinsztein DC, Leggo J, et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington's gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. *Am J Hum Genet*. 1996;59:16-22.
6. Sanchez A, Mila M, Castellvi-Bel S, et al. Maternal transmission in sporadic Huntington's disease. *J Neurol Neurosurg Psychiatry*. 1997;62:535-537.
7. Conneally PM. Huntington's disease: genetics and epidemiology. *Am J Hum Genet*. 1984;36:506-526.

8. Thomas M, Ashizawa T, Jankovic J. Minocycline in Huntington's disease: a pilot study. *Mov Disord.* 2004;19(6):692-695.
9. Verbessem P, Lemiere J, Eijnde BO, et al. Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. *Neurology.* 2003;61(7):925-930.
10. O'Suilleabhain P, Dewey RB Jr. A randomized trial of amantadine in Huntington's disease. *Arch Neurol.* 2003;60(7):996-998.
11. Huntington's Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. *Neurology.* 2003;61(11):1551-1556.

botulinum toxin type A.

Juvenile cases of Huntington's disease are often treated with carbidopa and levodopa to reduce prominent bradykinesia, posture abnormalities, rigidity, and dystonia.

Nutrition is important in Huntington's disease patients as their caloric requirements may be increased. At end stage, patients are bed-bound, mute and rigid. Eventually dysphagia and aspiration become problematic. The patient's wishes regarding gastric tube feeding should be ascertained in preparation for this stage of illness.

Pregnancy. Those who carry the gene should also have genetic counseling prior to conception. Prenatal diagnostic testing is available at some centers.

Conclusion. The last decade has seen exciting advances in the understanding of Huntington's disease.

Continuing research will also improve our ability to treat and possibly slow progression of the disease.

Address questions and comments to:

Pinky Agarwal, M.D.
 Lauren C. Seeberger, M.D.
 CNI Movement Disorders Center
 701 E. Hampden Avenue, #530
 Englewood, CO 80113