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DEPARTMENT OF NEUROLOGY

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Huntington's disease

Diagnosis

Huntington's disease (HD) is a hereditary brain disease, which disrupts thinking, mood, behavior, and movement. It is named after Dr. George Huntington, who first described the disorder in his essay, *On Chorea*, in 1872. HD occurs in all regions of the world and in all ethnic populations. In the United States, HD affects about 2 to 10 per 100,000 people, but in certain regions of the world, like Lake Maracaibo in Venezuela, and Moray Firth in Scotland, the prevalence is much higher. Both men and woman may inherit the gene that causes HD. HD usually begins in adulthood but may arise in children.

The disease usually starts in the 30s and 40s, but about 10 percent of HD cases have their onset before age 20 (juvenile HD). Juvenile HD typically presents with the combination of progressive parkinsonism (slowness of movements), dementia, incoordination, and seizures. In contrast, adult HD usually presents with the gradual onset of clumsiness, chorea, and cognitive and behavioral changes. Chorea is the main abnormal movement seen in HD. Chorea consists of involuntary, irregular, purposeless, abrupt, movements that flow randomly from one body part to another. The term derives from the Latin word for dance, but chorea is patternless, unlike most forms of dance. Chorea may be disabling because it interferes with voluntary movements, resulting in clumsiness, speech and swallowing difficulty, as well as loss of balance. Although chorea is the clinical hallmark of HD, other movement problems, such as dystonia (sustained muscle contractions resulting in abnormal postures), myoclonus (very rapid jerk-like movements), rigidity (muscle stiffness), and bradykinesia (slowness of movement) often co-exist.

Cognitive decline and various behavioral symptoms may start before the abnormal movements. Cognitive changes, manifested chiefly by loss of short-term memory, poor judgment, and impaired concentration, occur in nearly all patients with HD; however, some patients with late-onset chorea never develop dementia. On the other hand, the behavioral symptoms consist of personality changes, apathy, social withdrawal, anxiety, impulsiveness, depression, mania, paranoia, delusions, hostility, sleep disturbances, hallucinations, or psychosis.

Before the advent of a genetic blood test, the diagnosis of HD was based upon the typical clinical presentation and a positive family history of HD, supported by the findings of atrophy (shrinkage) of the caudate nucleus on brain imaging. Today, DNA testing can reliably diagnose HD and differentiate the disease from other disorders that cause similar symptoms. DNA testing is also available for family members of patients with HD who may not have symptoms but are at risk for the disease. However, because of potential psychological and legal implications of identifying a HD gene mutation in an asymptomatic, at-risk individual, predictive testing should be performed by a team of clinicians and geneticists who are knowledgeable about the disease and genetic techniques and who are sensitive to the psychosocial and ethical issues associated with such testing.

Cause

HD is a genetic disorder, inherited in an autosomal dominant pattern, which means that each child of an affected parent has a 50 percent chance of inheriting the disease-causing gene. Individuals who inherit the HD gene almost always develop the symptoms of HD, usually at the same age as their affected parent or earlier. The gene responsible for HD is *HTT*, which is located on the short arm of chromosome 4 (4p16.3). This gene produces a protein known as huntingtin, whose function remains unclear. The mutation that causes HD consists of an unstable enlargement of the gene's, which results in an abnormal elongation of the huntingtin protein. The abnormal huntingtin is toxic generates death of neurons with though various mechanisms. The part of the gene that is enlarged contains a repeats of three nucleotides (cytosine-adenine-guanine, or CAG). Normally, the

number of CAG repeats is less than 26, while in persons with HD the gene usually contains more than 40 repeats. Individuals with repeats ranging from 27 to 39 CAG repeats may rarely develop symptoms of HD, but they may transmit HD to their children because the number of repeats grows over successive generations. The degree of repeat expansion over a generation is usually greater when the gene is inherited from one's father. The number of repeats inversely correlates with the age at onset, such that children with HD may have 100 CAG repeats or more. Accordingly, young-onset patients usually inherit the disease from their father while older-onset patients are more likely to inherit the gene from their mother. There is no difference in the mean number of repeats between patients presenting with psychiatric symptoms and those with chorea and other motor disorders.

Treatment

There is no cure for HD. There are current studies in laboratory evaluating potential treatments targeting the DNA and RNA, such as the antisense strategy. However, those are not studied in humans yet. Among available medications, coenzyme Q10 was recently evaluated in a placebo-controlled study, and it did not slow the disease progression. Currently, the focus of the treatment is to improve the symptoms.

The treatment of chorea relays on drugs called dopaminergic depleters. They block the release of dopamine in the neuron terminals and modulate the control of movements. The advantage of these drugs is that they do not to cause late involuntary movements, called tardive dyskinesia. Tetrabenazine (Xenazine) was the first FDA approved medication for HD. Tetrabenazine might cause drowsiness, slowness of movement, and restlessness. Drowsiness is a common side effect and a common reason for patients to discontinue the medication. In addition, tetrabenazine requires a three times a day dosing due to its variable metabolism and short half-life. Prior to the drug's general FDA approval, Dr. Jankovic received special permission from the FDA (via an investigation new drug permit) to prescribe tetrabenazine in 1979 and has used the drug has since that time in well over a thousand patients, including those with HD.

More recently, deutetrabenazine (Austedo) was FDA-approved as an alternative for the treatment of chorea in HD. It contains a molecule called deuterium, which affects the drug metabolism and allows more prolonged medication duration and more stable blood levels. Deutetrabenazine requires twice a day dosing and the side effects were comparable with the placebo. Both tetrabenazine and deutetrabenazine had a warning of increased risk of depression and suicidality. Psychosis may improve with neuroleptics (drugs that block dopamine receptors), such as haloperidol, pimozide, fluphenazine, and thioridazine. These drugs, however, can induce tardive dyskinesia, and should only be used if absolutely needed to control symptoms. The atypical antipsychotics are preferred due to the lower risk of tardive dyskinesia. Clozapine, an atypical antipsychotic, may be a useful alternative to the typical neuroleptics, but the risk of agranulocytosis (a very low white cell count) complicates its use. Other atypical neuroleptics such as olanzapine (Zyprexa), quetiapine (Seroquel), and ziprasidone (Geodon) do not need close monitoring and may be easier to use, but are less effective in controlling chorea. Other medications for memory loss, depression and anxiety also may be useful in some HD patients.

The Movement Disorders Clinic at Baylor College of Medicine was designated as a Center of Excellence by the Huntington's Disease Society of America. It is also a member of the Huntington Study Group, a consortium of academic clinicians and researchers interested in finding the cause of neurodegeneration in HD and designing therapeutic trials of new medications.

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