

Hunting for Huntington's

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Huntington's disease (HD) is a well-defined, inherited neurodegenerative disease which afflicts the human population regardless of gender, race, or ethnicity. It results in significant morbidity and mortality.

It is inherited as an autosomal dominant disease that produces neuronal cell death in the basal ganglia, specifically the caudate nucleus. The neuronal cell death results in rigidity, involuntary movements, behavioural changes, and dementia. It is also called Huntington's Chorea (Chorea is Greek for dance), due to the characteristic movement disorder that is one of the hallmarks of the illness (Table 1).

Generally the onset of the illness is in mid-adult life. However, about 10% of sufferers develop it prior to the age of 20 (juvenile HD), and another 10% develop it after 55.

Clinically, the presentation of HD is categorized into adult onset and juvenile types, because the two presentations are very distinct.

Adult onset

In adult onset, HD clinically presents with the classic triad of motor disturbance, cognitive changes, and emotional symptoms. The early or prodromal phase of the disease may precede the onset of the classical disease by several years and can present with:

- slight personality changes,
- forgetfulness,
- clumsiness, and
- gradual development of brief fidgeting (movements of the fingers and toes).

The classical triad of HD is rigidity, chorea, and dementia and behavioural changes. It can best be described as follows:

Motor/movement disorder

The onset is very slow and insidious, presenting initially as clumsiness, fidgeting, and even as having balancing difficulties. The early symptoms of chorea, or the rapid, irregular, purposeless, jerky movements, can be confused with intentional movements. This confusion results in a delay of diagnosis. Very early, chorea may affect the peripheral areas (specifically fingers and toes). Later, chorea progresses centrally and involves the arms, legs, face, and trunk. By this time, the movements are much more pronounced and can be exacerbated further by stress or other emotional difficulties. As the motor disturbance becomes more widespread and generalized, it presents with slow, writhing, dance-like movements. By this time the movements flow into one another, having a slow and writhing quality (athetosis). In advanced stages of the disease, they have a more dystonic quality, leading to sustained muscle contractions, and present with unusual, twisting motions, and alternating or fixed postures.

The gait of a patient afflicted with HD is very distinct. This is usually characterized by unsteady, disjointed, and lurching movements and is often described as dance-like. The further progression of this affliction results in dysphagia, dysarthria, dysphonia, poor control of the tongue and diaphragm, postural instability, and clumsy fine motor movements.

Huntington's Disease

Table 1

Population at risk

Those at risk are individuals born into families with a history of Huntington's disease (HD). Some epidemiologic facts related to HD are as follows:

- The estimated prevalence rate is 5 to 10/100,000.
- Its incidence is 5 per 10,000.
- There are 30,000 people in North America who have an actual diagnosis of HD.
- Another 150,000 are "at risk" for developing HD because they have a parent with an established diagnosis of HD.
- In rare instances a person with no family history or a distant family history develops the disease through mutations in the "intermediate" allele.
- Homozygotes for the HD gene have also been described.
- European populations are at higher risk than African and Asian.

In the later stages of the disease, ocular abnormalities can result in abnormal saccades. In some patients, it can present with muscle stiffness (rigidity) and slowness of movements (bradykinesia).

Cognitive disorder

The early cognitive changes in HD can cause significant problems with functioning in the workplace and/or at home. The changes can be very imperceptible and can precede the movement disorder.

Initially, it presents with forgetfulness and difficulty sustaining attention and focus. Later, the cog-



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nitive faculties involving areas of comprehension, reasoning, memory, and judgment are affected. This presents in the form of difficulty with concentration, absorbing new information, problem-solving, communicating, impaired judgment, inappropriate responses, impaired communication, disorganized speech, and apraxia. Eventually the picture of dementia emerges.

The dementia is associated with:

- progressive disorientation and confusion,
- profound disintegration of an individual's personality, and
- devastating changes in memory which, along with restlessness, agitation, psychosis, and depression, lead to a variety of behavioural changes.

Behaviour disorder

The emotional and behavioural changes associated with HD may present before or after the onset of the motor disturbance. These changes involve:

- personality,
- perception,
- regulation,
- impulse control, and
- sexuality.

Some of the common behavioural changes are as follows:

Apathy: This leads to difficulties in initiation of conversation and a lack of desire for self-care.

Irritability and aggression: This is often very difficult to understand for the care providers and causes a lot of friction. The emotional volatility and explosiveness can lead to aggression towards the caregivers.

Anxiety: Patients with HD can be highly anxious and nervous about the diagnosis and the resulting loss of function. However, they may also present with the classical symptoms of a generalized anxiety disorder.

Depression: The presentation of depression is often considered to be reactive to the diagnosis of HD. Endogenous or major depressive episodes present with all the typical neurovegetative symptoms of depression that include depressed mood with sleep difficulties, diminished appetite, weight loss, fatigue, lack of motivation, impaired concentration, memory disturbances, reduced libido, anhedonia, and preoccupation with feelings of guilt, lack of self-worth, and suicide.

Obsessive compulsive disorder: This is due to the presentation of rigidity and inflexibility noted in HD patients. They rarely present with obsessions, compulsions, and magical thinking.

Disinhibition: This often leads to socially inappropriate behaviours, including sexually inappropriate behaviours. This is possibly related to impaired judgment.

Psychosis: Psychotic presentations, especially in the realm of depressive psychosis or manic psychosis, can rarely be the very first presentation of HD. Bipolar disorder or psychotic depression can present with the classical symptoms of hallucinations, delusions, impulsivity, agitation, affective dysregulation, disinhibition, and impaired judgment that are integral parts of these syndromes. Suicide and homicidal acts can also occur in the context of these disorders.

Eventually the disease has a fatal outcome. Death is usually a result of life-threatening complications, such as pneumonia or other infections, and injuries related to falls and choking.

Juvenile onset

This disease afflicts people under 20 and accounts for about 10% of all cases of HD. Adult onset and juvenile HD are quite different in their symptom presentation, even though they both are a result of the altered form of the Huntington gene (Table 2).

The gene is known to have paternal transmission, and more than 90% have an affected father. The juvenile form (Westphal variant) is more Parkinsonian in its presentation. It presents with prominent symptoms of rigidity, bradykinesia, and tremors, rather than chorea. Seizures, both generalized grand mal and partial types, are an additional hallmark of this disease. Myoclonic seizures have also been described in this population. Death usually occurs within 10 years of the age of onset. Juvenile HD differs from adult onset HD, but also shares some of the clinical features with its counterpart. (Table 3).

How is HD diagnosed?

The diagnostic workup in a patient suspected of having HD begins with a detailed and thorough history of the symptoms, and their duration and impact on the life of an individual and the caregivers. Also included is a detailed psychiatric history and family history. This is followed by a detailed and extensive physical, neurologic, and mental state examination. If a diagnosis of HD is suspected, consultation should be sought from an experienced neurologist, or the patient can be referred to the regional genetic clinic for further workup. Neuroimaging studies are helpful to delineate the pathologic changes in the caudate nucleus, other basal ganglia, and other structural changes in the brain on magnetic resonance imaging. Functional studies, like the positron emission tomography or single photon emission computed tomography scan, can also be helpful.

Genetic counselling is also essential. A definitive diagnosis can be made by using DNA analysis that employs the recombinant techniques involving polymerase chain reaction (PCR) and gel electrophoresis. Prenatal and presymptomatic testing of the pedigree is very important to identify family members who will develop this devastating illness later in life. Table 4 outlines the main diagnostic interventions.

Huntington's Disease

Table 2

Differences between juvenile and adult onset

	<u>Juvenile</u>	<u>Adult</u>
Prevalence	0.5-1/100,000	4-10/100,000
Inheritance	Autosomal dominant (80-90% inherit HD from father)	Autosomal dominant
Age of onset	Infancy to age 20	35-45 (rarely > 55)
Genetic changes	CAG repeats 80-100	CAG repeats 40-60
Progression of disease	Rapid	Slow
Early signs	<ul style="list-style-type: none"> • Declining school performance • Changes in handwriting • Difficulty learning new things • Movement problems • Co-ordination difficulties 	<ul style="list-style-type: none"> • Falls • Personality changes • Chorea • Decreased co-ordination
Later signs	<ul style="list-style-type: none"> • Rigidity • Bradykinesia • Generalized and partial seizures • Myoclonic seizures 	<ul style="list-style-type: none"> • Chorea • Psychosis • Depression • Dementia
Death	<ul style="list-style-type: none"> • Within 10 years of onset 	<ul style="list-style-type: none"> • Within 10-25 years of onset

What is the differential diagnosis?

HD can mimic other medical and psychiatric disorders, such as:

- hepatocerebral degeneration,
- schizophrenia with tardive dyskinesia,
- other choreas, or
- drug reactions

What is the treatment?

There is currently no known treatment available to prevent, cure, or slow down the progression of HD. The existing treatments we use today are primarily targeted at the management of the symptoms of HD. These include:

Table 4

Various diagnostic interventions

- Positive family history
- Neurologic examination
- Psychiatric examination
- Imaging studies
- DNA analysis using recombinant techniques, which employ
 - polymerase chain reaction
 - gel electrophoresis
- Predictive testing and counselling

Pharmacologic interventions

- Neuroleptics to treat psychosis and aggression
- Antidepressants for depression and obsessive compulsive disorders

Take-home message



- HD has a classical presentation in both the adult onset and juvenile onset types.
- HD ultimately leads to severe dementia and death.
- A definitive diagnosis of HD is established via the DNA analysis.

Table 3

Similarities between juvenile and adult onset HD

- Autosomal dominant inheritance
- Personality changes
- Severe movement disorder
- Dementia

- Anxiolytics for treatment of anxiety

Other treatments that are being studied are:

- Glucocorticoids
- Nonsteroidal anti-inflammatory agents
- Omega 3 fatty acids (now in experimental stage)
- Prostaglandins (now in experimental stage)
- Minocycline (now in experimental stage)

Physical therapies

Physical therapies are aimed at assistance with gait abnormalities and other motor disturbances.

Speech therapy

Speech therapy is used to help with communication and improving phonation with the use of certain assistive devices.

Experimental therapies

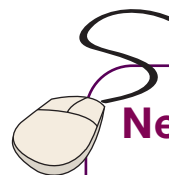
Other experimental treatments are being targeted at the various hypothesis formulated about the pathogenesis of HD. These include:

- removal of mutant protein buildup in the brain,
- geldanamycin agents aimed at targeting the various neurotransmitters,
- bromocriptine, tiapridal, cholinergic agents, gaba-

- aminobutyric acid approaches, etc., and
- N-methyl-D-aspartate blockage. [CME](#)

References

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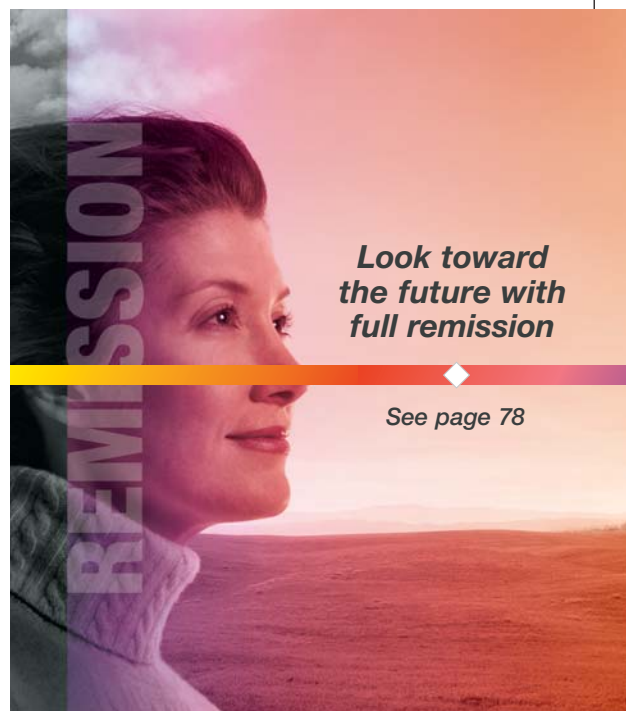
Net Reading

Huntington Society of Canada:
www.hsc-ca.org

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