Huntington Disease
Pathogenesis and Treatment

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KEYWORDS

• Huntington • Chorea • Huntingtin • Polyglutamine • Striatum • Pathogenesis • Neurodegeneration • Treatment

KEY POINTS

- Huntington disease (HD) is an autosomal dominant inherited neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline, ultimately culminating in death.
- Mutant huntingtin protein alters neuronal function via multiple intracellular mechanisms. Striatal neurons in particular are selectively vulnerable to these toxic effects, and degenerate in a sequence, which helps explain the evolution of chorea and other motor features.
- Although there is currently no direct treatment of HD, chorea and psychiatric symptoms often respond to pharmacotherapy. A better understanding of HD pathogenesis, as well as more sophisticated clinical trials using newer biomarkers, may lead to meaningful therapeutic advances.

OVERVIEW

Huntington disease (HD) is an autosomal dominant inherited neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline, resulting in death within 15 to 20 years after diagnosis.[1] In the United States and Canada, approximately 30,000 people carry the diagnosis and an estimated 150,000 more are at risk. HD is most prevalent in people of European descent; approximately 10 to 15 per 100,000.[2,3] Men and women are equally at risk. Median age of diagnosis approximates 40 years, with a wide range in age of onset. Onset before age 20 years or after age 65 years is rare. The combination of typical midlife onset and dominant inheritance affects entire families across the social scale, and devastates the lives of patients, at-risk individuals, and genetically normal family members alike. Management options at this time are limited, and there is still no therapy to slow down the inexorable loss of function.

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The pathologic mutation consists of an expanded CAG repeat in the *huntingtin* gene (HTT) on chromosome 4, encoding the huntingtin (htt) protein,[4] resulting in an excessively long polyglutamine stretch near the N-terminus of this protein. In the general population, there are on average 17 to 20 CAG repeats in the HTT gene.[5] With 40 or more repeats, a person develops HD with 100% certainty, but with repeats of 36 to 39, there is incomplete penetrance. CAG repeat lengths of 6 to 26 do not cause disease and are thus considered normal. The intermediate range, from 27 to 35 repeats, does not cause HD, with a few reported exceptions.[6] It is notable that all alleles of 27 repeats and higher are unstable and prone to expand in future generations, particularly when transmitted by a male parent. Although most patients with HD have an affected parent, up to 10% of cases may result from new expansions into the disease range.[7,8] The appearance of earlier and more severe symptoms in successive generations caused by intergenerational repeat expansion is known as anticipation.

This article highlights the current knowledge of pathogenesis and treatment. It begins with a review of the clinical features.

CLINICAL FEATURES

The typical clinical triad in HD is (1) a progressive motor disorder; (2) progressive cognitive disturbance culminating in dementia; and (3) psychiatric disturbances including depression, anxiety, apathy, obsessive-compulsive behaviors, outbursts, addictions, and occasionally psychosis. Weight loss is a common feature. Note that a diagnosis of HD is made only when the characteristic motor features are apparent. By convention, gene-positive individuals without motor features are considered premanifest, even though there is an accumulation of subclinical and imaging anomalies in such individuals (discussed later).

Motor Disorder

Although chorea is only a small part of motor dysfunction in HD, it remains its most recognizable feature. Chorea often begins as fleeting, suppressible, random fidgety movements, seen best in the distal extremities. With time, chorea becomes more overt, involving larger and more proximal muscles. Most patients with chorea are not aware of the extent of their involuntary movements; some deny them altogether. Particularly violent chorea is indistinguishable from ballism and may result in exhaustion or falls.

Saccadic eye movement abnormalities occur early and persist throughout the disease. Saccades are slow to initiate, often requiring a head movement or a blink to break fixation; saccade velocity may slow.[9]

Ataxia of speech, limbs, or gait can occur as the disease advances. Dystonia, which is a more sustained posturing or twisting, is common. Bradykinesia is common in HD and refers to slowness and reduced scaling of movement, such as diminished facial expression; reduced spontaneous gesturing; small, hesitant finger taps; reduced arm swing; and small steps.

There is considerable heterogeneity in motor findings from patient to patient. Juvenile patients with HD may lack chorea and present with bradykinesia and rigidity; this is known as the Westphal variant of HD. Even within the disease course of an individual patient with HD, the motor abnormalities evolve: chorea early in the disease may give way to superimposed dystonia as the disease progresses,[10] culminating in striking bradykinesia, rigidity, and poor postural reflexes in late stages.

Progressive motor failure is a major cause of life-ending complications. Dysphagia contributes to weight loss and aspiration, and falls and serious injuries become increasingly common.