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.

Cognitive Disorder

Dementia is an underappreciated facet of HD, and is especially serious because it develops in the prime of life, disrupting social and occupational functions. Initial difficulties affect multitasking, focus, short-term memory, and learning new skills. A recent large-scale prospective observational analysis of premanifest persons[11] showed declines in several measures, including working memory, attention, and verbal fluency, consistent with prior smaller studies. These deficits were worse for subjects approaching their expected motor onset. By the time of diagnosis, most subjects with HD have cognitive impairment clearly evident on neuropsychological testing.

Over many years, cognitive impairment eventually progresses to frank dementia. Unlike Alzheimer dementia, HD dementia is largely subcortical, marked by slow thought processes and executive dysfunction, and problems with attention and sequencing.[12,13] Although impaired, episodic memory is better preserved than in Alzheimer dementia, as is language function.

Individuals with HD often show striking lack of insight into their own cognitive and motor symptoms, even when these are obvious to others.[14] This lack of insight may reflect dysfunction of striatal neurons receiving prominent frontal lobe inputs.

Psychiatric Disorder

For many patients with HD and their families, behavioral problems are the most vexing. These problems range from affective illness to anxiety disorders to delusional behavior and, rarely, hallucinations.[15,16] Psychiatric features and their severity vary greatly, and do not correlate with chorea or dementia.[15]

Most patients experience some behavioral symptoms before their diagnosis[17–19]; most common are depression, obsessive-compulsive behaviors, irritability, and outbursts.[17,18] Personality changes may occur for years before the diagnosis, although this may be apparent to families only in retrospect.

Up to 50% of patients are depressed at some point in the disease.[20] Apathy is also common, although it is more difficult to treat. Compulsive behaviors in HD may resemble the cognitive rigidity and perseveration typical of frontal lobe disorders, and probably reflect striatal dysfunction.

There is a high rate of suicide in gene-positive individuals, both before and after diagnosis.[21,22]

PATHOGENESIS

This article reviews HD pathogenesis in a progressively reductionist sequence: (1) considerations pertaining to the organism and the brain as a whole, (2) a discussion of striatal disorders specifically, and (3) a review of genetic and molecular pathogenesis. Clinical correlations are provided where possible.

HUNTINGTON DISEASE PATHOGENESIS AT THE WHOLE-BRAIN AND ORGANISM LEVELS

The htt protein is expressed by neurons throughout the central nervous system (CNS) without dramatic regional differences. Despite this, there is a regional pattern to HD on pathology.[23] Although classically described as a striatal degeneration, widespread brain degeneration is apparent in late-stage autopsies. Gross striatal atrophy is prominent, but thinning of the cortical mantle and low brain weights and volumes are documented well. Careful studies reveal neuronal loss in many regions, including the neocortex, cerebellum, hippocampus, substantia nigra, and brainstem nuclei. There

is also diffuse loss of cerebral white matter. These findings correlate well with the many clinical deficits in advanced HD, including pyramidal signs, ataxia, dysarthria, dysphagia, incoordination, and dementia.

Recent work has helped clinicians to better understand HD pathogenesis at the whole-brain and regional levels. Volumetric MRI analyses, performed in ongoing large prospective studies of at-risk individuals, reveal that the most clearly measurable and progressive atrophy affects the striatum and global cerebral white matter.[24,25] These changes occur well before the earliest typical motor features. Cortical atrophy also occurs in asymptomatic subjects,[26–28] changing quantitatively over short intervals (2–3 years), consistent with histopathologic findings of early neocortical degeneration.[23] There is interest in developing such MRI analyses as biomarkers for use in future clinical trials with premanifest subjects.

Weight loss is common in HD, even in the earliest manifest stages.[29] At least some of this might be attributed to hyperkinesia. However, disordered somatic and brain development caused by mutant htt might occur even as early as early life. In a comparison study of at-risk children, those with an expanded allele had modestly lower weight and body mass index, and a smaller head circumference, than those with normal alleles.[30] In another study of premanifest adults who underwent predictive testing, a subtle reduction in intracranial volume was shown for expansion-positive individuals versus their expansion-negative counterparts.[31] If confirmed, such results would be consistent with a purported role for htt in development and metabolism, along with its broad expression in human tissue (discussed later).

The mechanisms for selective involvement of the striatum have been best studied, and are described next.

HUNTINGTON DISEASE PATHOGENESIS AT THE STRIATAL LEVEL

Disproportionate striatal degeneration early in the disease was described decades ago.[32] Within the striatum, neurodegeneration progresses in caudal to rostral and dorsal to ventral gradients. Initial explorations of HD striatal disorders suggested loss of intrinsic gamma-aminobutyric acid (GABA)ergic and cholinergic neurons with relative sparing of extrinsic dopaminergic terminals. PET imaging research in HD has shown declines in striatal neurotransmitter markers (particularly dopamine receptors) that occur very early.[33–35] The striatum receives massive glutamatergic input from the cortex and thalamus, and has been shown to be particularly susceptible to the postulated excitotoxic effects.[36–38]

Intrinsic striatal neurons are differentially affected. There are 2 major populations: (1) aspiny interneurons whose projection arbors are restricted to the striatum, and (2) GABAergic medium spiny projection neurons whose primary axons synapse in targets downstream of the striatum. The best studied aspiny neurons are cholinergic, which are virtually spared in HD.[39] However, striatal choline acetyltransferase levels decline markedly, suggesting significant striatal cholinergic interneuron dysfunction, even in the absence of degeneration. At least 1 other population of striatal interneurons, those cocontaining somatostatin and neuropeptide Y and expressing high levels of nitric oxide synthase, are spared in HD. Recent work has identified progressive depletion of parvalbuminergic interneurons; this is a possible explanation for the emergence of dystonia as HD advances.[40]

Subpopulations of medium spiny projection neurons are defined by their primary projection targets, coexpressed neuropeptides, and neurotransmitter receptors. Segregated pools of these neurons project to the external segment of the globus pallidus (GPe), internal segment of the globus pallidus (GPi), substantia nigra

dopaminergic pars compacta, and substantia nigra GABAergic pars reticulata (SNr). Striato-GPe neurons express enkephalins, dopamine D2 receptors, and adenosine A2a receptors, whereas the other striatal projection neuron pools tend to express tachykinins and dopamine D1 receptors. Examination of postmortem HD material suggests a sequential pattern in degeneration of striatal projection neuron subpopulations. The early changes seem to be loss of striato-GPe neurons and perhaps striato-SNr neurons,[41–43] whereas striato-GPi neurons are spared until late.

This temporal order of neuronal loss correlates broadly with features of the natural history of HD. Because basal ganglia inputs to the superior colliculus come from SNr, the early loss of striato-SNr projection neurons correlates well with early saccadic abnormalities. The evolution of involuntary movements in HD also has neuropathologic correlates. Initial degeneration of striato-GPe neurons results in inhibition of the subthalamic nucleus. Diminished subthalamic activity is associated with chorea. In many patients, disease progression is associated with gradual worsening of chorea, which then peaks in intensity and gradually declines, only to be accompanied by worsening dystonia and bradykinesia. In these later stages, there is generalized loss of striatal projection neurons and probably neurons within other nuclei of the basal ganglia.[44] In one study of a marker of striosomal striatal projection neurons in a broad spectrum of HD postmortem specimens there was a correlation between disordered mood and striosomal disorders.[45]

The ultimate cause of HD neurodegeneration, regardless of regional patterns, is the expanded HTT gene and its transcribed product.

HUNTINGTON DISEASE PATHOGENESIS AT THE GENE AND PROTEIN LEVEL

The htt protein is very large (359 kD) and expressed widely in the CNS and in other tissues. In neurons, it is found largely in somatodendritic and axonal cytoplasm, and interacts with many other proteins. Htt is essential for early neuronal development, but its precise functions in adults are unclear.

There is a wide range of age of onset and symptom features in HD. CAG repeat length is a major factor, correlating inversely with age of onset.[46–49] For unclear reasons, the rarer highly expanded repeats (>60) result in uniformly young age of onset. However, for the more common smaller repeat lengths (<45) there is much larger variance in age of onset. Other genetic and environmental factors, as yet unknown, must also contribute to age of onset. Repeat length also influences motor phenotype, because early-onset disease is more likely to present with prominent dystonia and bradykinesia, although this may reflect the impact of the mutant allele on developing brains.

It is unclear whether repeat length influences the rate of disease progression. Although some studies have found no correlation,[47] other studies have.[50] Age may have been a confounder; a more recent analysis showed a stronger correlation between longer repeats and faster decline after adjusting for age.[51] Familial aggregation of certain symptoms (eg, psychosis) occurs in HD and this likely reflects genetic modifiers.

An expanded allele of intermediate length (27–35 repeats) may not be benign. A prospective observational study showed that such individuals, who were unaware of their own allele status, had a higher rate of apathy and suicidal ideation compared with subjects with normal repeat lengths.[52] Cases have been reported of a syndrome indistinguishable from manifest HD in individuals whose repeat length was within this intermediate range.[6]

Most evidence points to a toxic gain-of-function role for mutant htt (mhtt) in causing the disease, although some loss of function may contribute. There is emerging evidence of abnormal transcription of the expanded HTT allele. Aberrant splicing may

produce a truncated mRNA that only codes for exon 1, which contains the polyglutamine domain.[53] Even when the full mutant protein is transcribed and translated, protease activity can lead to the formation of shorter N-terminal fragments containing the mutant polyglutamine expansion.[54] Posttranslational modification may modify toxicity, via phosphorylation, acetylation, and conformational changes.[55]

Regardless of how these short mhtt fragments are formed, they are likely toxic as individual molecules or as oligomers. Larger aggregates become visible in the cytoplasm or nucleus,[56] although these may be compensatory or incidental rather than pathogenic. Studies of animal models as well as human brain tissue have identified several key mechanisms whereby mhtt fragments could be toxic to the cell (summarized in **Box 1**)[55,57]:

1. Transcriptional interference. Mhtt can enter the nucleus, and is thought to directly perturb gene transcription. Altered transcription has been shown for multiple other genes,[58,59] notably neurotransmitter receptors and ion channels,[60,61] and BDNF.[62]
2. Cytoskeletal disruption. Htt has many interactions with cytoplasmic proteins, some of which function closely with the microtubule system, and thus may regulate vesicular transport.[63,64] Mutant htt could cause such trafficking to fail.
3. Protein mishandling. Directly or indirectly, mhtt may overwhelm the neuron's ability to tag and clear degraded and misfolded proteins via the ubiquitin-proteosome[65,66] and autophagy-lysosome[67,68] systems.
4. Altered mitochondrial dynamics. Messenger RNA levels of numerous mitochondria-associated proteins are altered in HD brains.[69] Mhtt seems to reduce the transcription of PGC-alpha, itself a key transcription regulator that activates many genes important in the structure and function of mitochondria.[70,71] Neurons in regions most affected by mhtt show altered high-energy phosphate stores, including reduced ATP levels[72] and evidence of oxidative stress.[73] Brain metabolic

Box 1
Key intracellular mechanisms for neurodegeneration in HD, and the likely role of the disease mutation therein. See text for details and citations

HD Pathogenetic Mechanism	Explanation	Role of Disease Mutation
Transcription interference	Critical neuronal proteins and transcription factors are overexpressed or underexpressed	Gain of function and haploinsufficiency
Cytoskeletal disruption	Impaired trafficking of organelles and vesicles within the neuron	Gain of function and haploinsufficiency
Protein mishandling	Ubiquitin-proteosome and autophagy-lysosome systems cannot effectively tag and clear aggregated and misfolded proteins	Gain of function
Altered mitochondrial dynamics	Mitochondrial function is impaired, resulting in imbalance of cellular metabolites, and oxidative stress	Gain of function
Excitotoxicity and disturbed calcium homeostasis	Excess NMDA receptor sensitivity to glutamatergic input, and increased calcium permeability, promote cell death	Gain of function

Abbreviation: NMDA, *N*-methyl-D-aspartate.

deficits have been shown in patients with HD via magnetic resonance spectroscopy and increased cerebrospinal fluid lactate levels.[74]

5. Excitotoxicity and disordered calcium signaling. Numerous studies have implicated glutamatergic stimulation of *N*-methyl-D-aspartate (NMDA) receptors as a proximate cause in HD neurodegeneration, particularly within the striatum.[36–38] Mhtt directly sensitizes NMDA receptors via the NR2B subunit.[75,76] Mhtt also seems to interact with the inositol triphosphate receptor type 1, which is a major calcium channel in neuronal membranes.[77] These changes result in excessive calcium influx, stressing the neuron and ultimately pushing it toward apoptosis and death.[36,75,77]

Given strong experimental evidence for all these mechanisms, it is highly possible that pleiotropic toxic effects of mutant htt are responsible for neuronal degeneration. Different mechanisms may be more important in different neuronal populations. Other potential mechanisms, such as aberrant cholesterol metabolism and even RNA toxicity, have been proposed. A better understanding of these complex cellular events, including their timing in a person's life, their sequence, and their associated feedbacks, may be forthcoming. This understanding will enable clinicians to better understand the selective vulnerability of different brain regions and cell populations, and better explain the clinical features and course; most importantly, it may lead to the development of more effective therapies. For example, major ongoing multicenter trials are testing coenzyme Q10 and high-dose creatine; compounds that support mitochondrial function and might delay disease progression.

Many of the themes described earlier are common to other forms of neurodegeneration, including Parkinson disease and Alzheimer disease. However, in HD there is a clearly established starting point: the mutation of a single gene. Studying the pathogenesis of HD may therefore help clinicians to improve not only the lives of those who have it but also the lives of those who have other brain degenerations.

MANAGEMENT

HD has no cure. Furthermore, there is no known therapy that slows the degeneration or the rate of clinical decline. This unmet need is a major area of HD research. Some symptoms can be treated pharmacologically, and others can only be addressed via nonpharmacologic supportive measures (summarized in **Table 1**).

Symptomatic Pharmacotherapy

HD symptoms respond variably to medications. In general, psychiatric symptoms are perhaps the most amenable to pharmacotherapy. Of motor symptoms, chorea is the most readily responsive. Cognitive symptoms and dementia are the least responsive.

Many patients with chorea are not aware of their involuntary movements or are not impaired by chorea. In these cases, reassurance and education (especially of family members) is important. When chorea does require treatment because it affects a patient's quality of life, function, or safety, it responds best to medications that reduce dopaminergic neurotransmission. In the past, dopamine receptor blockers have been most commonly prescribed. Examples include haloperidol, risperidone, and olanzapine. These agents have the advantage of augmenting treatment of depression, and helping with irritability, outbursts, and psychosis. A disadvantage is that typical and atypical antipsychotics increase the risk of sudden cardiac death.[78] The other major option for chorea is the dopamine-depleting agent tetrabenazine, which reduces chorea in a dose-dependent manner.[79] However, this agent depletes other catecholamines, including serotonin and norepinephrine, so it is best avoided in individuals

...ns, both pharmacologic and nonpharmacologic, in the management of the commonest HD symptoms and complications. See text for details and citations

HD Symptom or Complication	Therapeutic Intervention
Chorea	Dopamine depletion (tetrabenazine) Dopamine receptor blockers Amantadine
Parkinsonism and rigidity	Levodopa (juvenile HD)
Dysarthria	Speech therapy
Dysphagia	Speech and swallow therapy Dietary modification
Gait impairment and falls	Physical therapy Assistive devices Home modification
Depression	SSRIs Other antidepressants
Anxiety	SSRIs Buspirone
Obsessive-compulsive behaviors	SSRIs
Outbursts and impulsivity	Antipsychotics Mood-stabilizing anticonvulsants
Delusions and hallucinations	Antipsychotics
Apathy	Structured routine and cues
Cognitive dysfunction and dementia	Structured routine and cues
Weight loss	High-calorie supplements Dietary consultation
Caregiver burden and family stress	Social work services Individual and family therapy Respite care

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

with significant depression or anxiety. Tetrabenazine may worsen dysphagia. All of these therapies may worsen gait and bradykinesia, or cause somnolence.

Other medications (eg, amantadine) have been reported as modestly beneficial for chorea.[80,81] Bradykinesia and rigidity in younger onset individuals can respond to dopaminergic agents used in parkinsonism.[82] Myoclonus, which is rare in HD and is sometimes mistaken for chorea, can respond to valproic acid.[83]

There is a lack of clinical trials for psychiatric treatments in HD specifically.[84] Most experts agree that depression in HD often responds well to antidepressants; most commonly selective serotonin reuptake inhibitor (SSRIs). Obsessive-compulsive behaviors, anxiety, and irritability may also respond to SSRIs. Mood stabilizers such as valproate and carbamazepine may help with emotional lability and impulsivity. Buspirone may help with anxiety. Antipsychotics, both typical and atypical, may help with psychosis, delusions, and agitation, but doses should be maintained at a minimum to reduce the risk of extrapyramidal side effects. Apathy is the target of an ongoing clinical trial of bupropion.[85]

Thus far, limited trials of cognitive enhancing agents used primarily in Alzheimer disease, such as memantine,[86] rivastigmine,[87] and donepezil,[88] have shown only questionable benefit.

Deep brain stimulation has been performed on isolated subjects with severe chorea in HD.[89,90] Follow-up reports indicate benefit for chorea, but it is not always sustained, and there is no evidence of benefit for other motor and cognitive-behavioral symptoms.

Nonpharmacologic Management

Comprehensive care in HD draws from a range of professionals: primary care physicians, neurologists, psychiatrists, geneticists, physical and occupational therapists, speech pathologists, nutritionists, social workers, and counselors. Nondrug interventions are a critical part of HD management.[91]

Physical and occupational therapy are important in HD care. Gait assist devices (such as walkers) and home safety improvements (eg, hazard removal, grab-bars, shower chairs) are also valuable. Speech therapists can evaluate and palliate dysarthria and dysphagia; options include exercises and food consistency modifications. Distractions should be minimized during mealtimes so that patients can concentrate on the mechanics of eating and swallowing. Dietary consultation can be a valuable adjunct in dealing with weight loss; high-calorie supplements are often used.

Behavioral symptoms such as apathy and cognitive problems such as executive dysfunction can be ameliorated via structured daily schedules, cues, and regular routines. Daytime respite care may provide a social outlet for patients and relieve caregiver burden. Family members of all ages struggle with the interpersonal, financial, and social stresses of this disease, so clinicians must remember the value of social work services, as well as individual or family counseling services. Even in advanced HD, clinicians must assume that a patient's recognition and comprehension are preserved; severe dysarthria, rigidity, and bradykinesia can make patients appear more cognitively impaired than they really are, leading to frustration and a loss of dignity. Clinicians and family members must avoid talking over the patient.

The efficacy of many nonpharmacologic interventions is often limited by the patient's cognitive and behavioral status. As with many aspects of HD, the burden of maximizing benefits from supportive interventions is placed on caregivers.

SUMMARY

HD is a relentlessly progressive inherited polyglutamine neurodegeneration causing severe cognitive, motor, and psychiatric disability in the prime of life. It is fatal in most cases. Although many of its clinical characteristics can be explained by pathology of the striatum, and its connections to the frontal lobes, HD is no longer simply considered a basal ganglia disorder. Subtle but measurable markers of global brain degeneration emerge even before the motor symptoms manifest, as revealed by volumetric imaging and cognitive batteries. In retrospect, this is not surprising, given the wide expression of the htt protein, and its many important interactions within the neuron.

Current treatment is limited to symptomatic pharmacotherapy for behavioral disturbance and chorea, and other supportive care. A major goal of current research is to identify disease-modifying therapy. Improved understanding of the genetic and molecular pathogenesis may lead to newer drug candidates with greater chances of success.

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