Huntington's Disease

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Niall P. Pender and Walter J. Koroshetz

Abstract Huntington's disease (HD) is an autosomal dominant neurodegenerative brain disorder. The mutation was identified in 1993 as an expanded CAG repeat that codes for an abnormally high number of glutamines in the huntingtin protein. At present, there is no known treatment to slow the pace of neurodegeneration, which generally leads to death over a 20-year period after clinical diagnosis. The clinical manifestations of the disease vary widely but they generally include dysfunction in cognition, mood, voluntary motor control, and most patients have the signature finding of chorea.

Keywords Huntington's disease • Chorea • Huntingtin (protein) • CAG repeat • Neurodegeneration • Neurogenetic (disorder) • Presymptomatic genetic testing • Motor control • Neuropsychiatric • Cognitive disorder • Behavioral difficulties

Introduction

Huntington's disease (HD) results from an expansion of the trinucleotide repeat (cytosine adenine guanine; CAG) at a gene on chromosome 4. While there is no unique set of symptoms, which indicate the onset in HD, many patients present initially with symptoms that reflect early neurological impairment, such as brief random irregular muscle jerks (chorea), writhing movements (athetosis), difficulty walking, and a tendency to fall or clumsiness. Many also present with a range of psychiatric problems including depression and anxiety. The rate of suicide in patients with HD is higher than normal base rates and accounts for 7% of deaths in nonhospitalized HD patients and 1.8–5.3% among individuals at 50% risk. There are also reports of self-injury, alcohol abuse, criminal offences, and marital difficulties. Cognitive impairments such as poor short-term memory, poor concentration, deterioration in work performance, and poor judgement have been noted in the early stages. As a result of degeneration in the fronto-striatal regions leading to behavioral disinhibition,

W.J. Koroshetz (✉)
Neurological Disorders and Stroke Institute,
National Institutes of Health, Bethesda, MD, USA
e-mail: koroshetzw@mail.nih.gov

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patients can become aggressive or violent as the disease progresses. It has been recognized that the initial site of deterioration in HD lies within the basal ganglia and that as the disease progresses, the damage extends to encompass the cortical structures.

Clinical Course

HD is rare but usually develops in patients between ages 30 and 50. The age of onset does, however, vary from 2 years to mid 80s. It has been estimated that over 25% of cases begin after the age of 50 years, whereas 7% begin before 20 years of age.

As an autosomal dominant condition, the disease has almost equal prevalence in males and females but a marked variability in the age of onset both within and between families has been noted. As the CAG repeat is unstable in spermatogenesis, inheritence of a longer repeat expansion leading to apparent sporadic cases and earlier age of onset is associated with transmission of the HD gene throughthe male line of a family.

Since the genetic test became available, it has been observed that only between 40% and 79% of individuals at risk for the condition reported an intention to take the test. However, careful genetic counselling and pretest screening is essential to manage the numerous ethical and psychological consequences of preparing to take such a test.

As the mutation is present from birth and the condition is slowly progressive, the precise onset of disease may be difficult to identify. By convention, the disorder is usually diagnosed when chorea manifests. However, most patients have changes that predate chorea, which are frequently detected by close family members, some of whom have witnessed similar changes in the parent or siblings. The early changes may be in behavior, memory, mood, speech pattern, facial expression, or gait and posture. Drop in job performance and marital discord can lead to major upheaval in those who have inherited the mutation but do not yet have chorea.

Table 8.1 lists the most common measures of disease progression and functional capacity for the clinic.

Table 8.1 Common measures of functional disability and disease progression

Title	Authors	Scale description
Functional Capacity Rating Scale	Shoulsan and Fahn (1979)	Measures functional capacity across five domains on a scale of 1–5
Unified Huntington's Disease Rating Scale (UHDRS)	Kieburtz and Huntington's disease study group (1996)	A multi-domain measure of disease progression across six domains of function. Includes a Functional Assessment and Total Functional Capacity Scale
Core Assessment Program for Intracerebral Transplantation in Huntington's disease (CAPIT-HD)	Quinn et al. (1996)	A multi-domain assessment protocol originally developed for the transplantation program

The course of Huntington's disease can nevertheless be variable. The average age of motor onset is around 42 years but HD can begin in childhood or even in the elderly. The extremes of onset age are determined in large part by the inherited CAG repeat length. Normal individuals have repeat lengths less than 32 in the huntingtin gene; persons with Huntington's disease generally have repeat lengths greater than 36, but frequently of 40–50. Childhood onset of disease is usually caused by an especially large CAG repeat (i.e., >50).

Children affected by HD generally present with a bradykinetic form of the disease and appear parkinsonian. They may have seizures. Generally, the first signs are related to drop in school performance. In rare families, parents of affected individuals do not have clinical evidence of disease despite living to an advanced age. The parents in these families have repeat lengths in the intermediate range, between 32 and 36. Their symptomatic offspring, however, have mutations with longer repeat lengths. When this occurs, the disease gene is generally inherited from the father. This "anticipation" occurs due to an expansion of the unstable CAG repeat in the development of the sperm.

More commonly, disease onset is in midlife. The individual with early signs of HD has grown up in a family in which one of the parents became affected and the parent may have passed through the course of the disease and died. The newly affected individual's family life may have been severely disrupted during their childhood by the parent's change in behavior. The psychological stress in such persons is difficult to underestimate. They, and their siblings, have been dreading the 50/50 chance that they will become affected. For example, benign myokymia is often misinterpreted as chorea. A fall or stumble can precipitate a fear that the disease has come. Depression and suicide rates are increased in persons at risk for HD even in the years before the diagnosis. Therefore, the physician treating a patient with Huntington's should be sensitive to the fears and complaints of the family, including at-risk siblings and offspring.

Prevalence

Prevalence rates have varied within and between countries, but the prevalence has been thought to range between 5 and 10/100, 000. A higher prevalence has been reported in South Wales and Venezuela as compared to a lower rate found in Finland, Japan, and African-American populations. This variability is due, predominantly, to the relative mobility of carriers of the gene and the existence of isolated "pockets" of families living in close proximity.

Pathology

Huntington's disease causes progressive brain atrophy. There is a particularly severe degeneration of the caudate nucleus that begins in the tail of the caudate and then affects the most dorsal medial aspect. Eventually, the caudate atrophies to a thin tissue paper-like

gliotic structure that is devoid of usually predominating medium spiny neurons. This gives a box car appearance of enlarged lateral ventricles on computed tomography (CT) scan. There is also much more widespread brain degeneration with cortical loss, white matter loss, and extensive gliosis (Fig. 8.1). Remaining neurons in multiple brain regions show intranuclear inclusions of the huntingtin protein. Like many neurodegenerative disorders, Huntington's disease is associated with abnormal protein accumulation and misfolding of the accumulated proteins. The role of non neuronal cells is gaining support in both HD and ALS. In both cases genetic animal models with the mutation in microglia or glial cells but not neurons is associated with pathologic changes.

Symptomatology

Huntington's disease is associated with a triad of difficulties including the movement disorder as well as cognitive and neuropsychiatric conditions. Each of these is associated with a complex set of psychosocial problems. Patients with Huntington's disease face a range of difficulties from diagnosis to death and these difficulties are not confined to the patient themselves but also to the family. As an autosomal dominant disorder, the disease has a particular resonance with families of sufferers.

Movement Disorder

By the time that chorea manifests, Huntington's disease generally includes some alteration in voluntary motor control. The ability to make rapid, repetitive, sequential movements is often abnormal.

Tests such as alternately tapping the thumb against the tips of the fingers, repetitively tapping the tip of the tongue against the top lip, alternately tapping the top, then the palm of one hand against the palm of the other hand all show slowing and irregularities in timing. There is generally great difficulty keeping the tongue protruded over a short, i.e., 10 s period.

Eye movement abnormalities are common. These include inability to make smooth pursuits due to intrusive saccades and delays in initiation of saccades. There is also dramatic slowing of saccadic velocity in some patients.

The gait of the person with early Huntington's disease demonstrates increased variability in step length and distance from the intended path. Inability to maintain position after gently pulling the patient backward, and trouble performing tandem walking is common. Though the cerebellum is generally spared, the finger to nose test and heel to shin test generally shows dysmetria.

Chorea, from the Greek for dance, often starts as a quick flick at multiple joints in the fingers or fingers and wrist while walking. It commonly worsens to twisting turns of the limbs, involuntary neck and facial movements, with blinks, and writhing tongue movements. The progressive involvement of lingual and bulbar control leads to dysarthria and dysphagia. Food with a soft, moist consistency such as pudding is easiest to swallow. Maintaining adequate nutrition can be challenging and motor symptoms tend to worsen

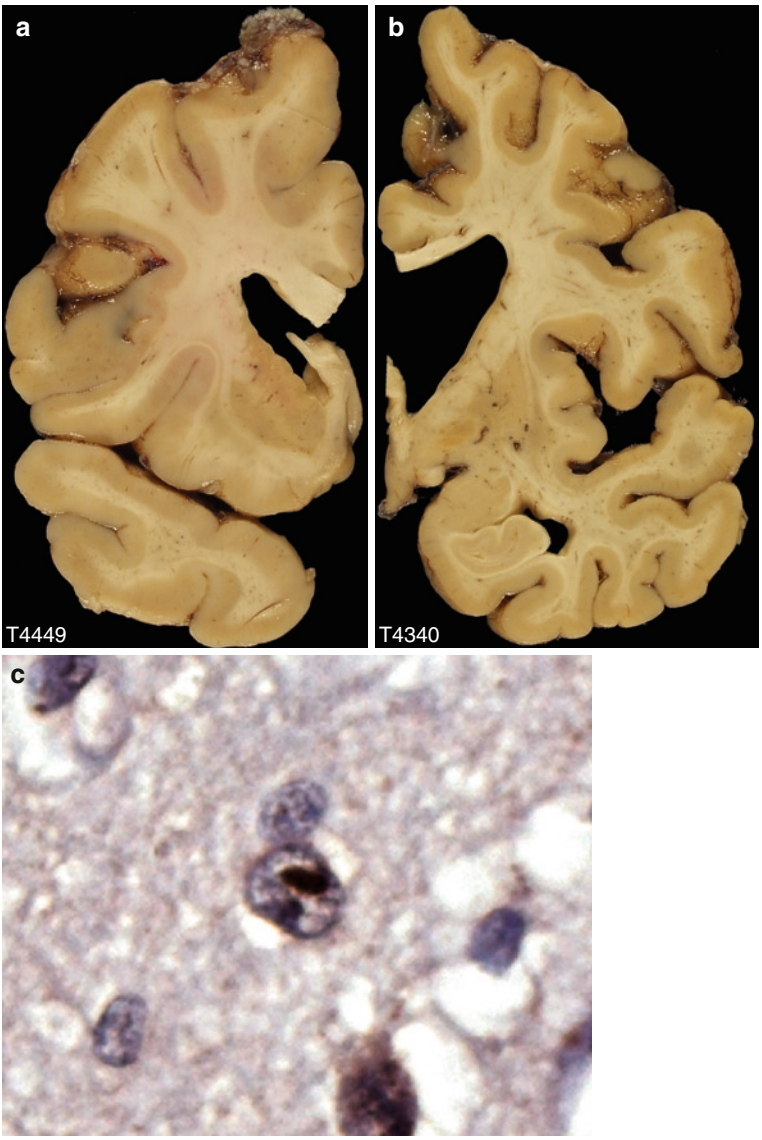

Fig. 8.1 Neuropathology of Huntington's disease. (**a**) The caudate nucleus bulges into the ventricle in normal individuals but is flattened in this 55-year-old person dying with Huntington's disease as seen in this coronal section through one brain hemisphere. Characteristically, the atrophy is more severe in the dorsal aspects of the caudate. (**b**) The caudate is barely visible in this 75 year old with severe degeneration of the caudate and globus pallidus. (**c**) The center neuron contains a classic intranuclear inclusion composed of aggregates of the mutant huntingtin protein (Courtesy of Dr. Jean Paul Vonsattel of Columbia University)

as patients lose weight. Most become almost mute in the later stages of the illness and are completely unable to swallow without aspirating. Chorea, which can be of large amplitude and forceful enough to cause self-injury, tends to slow over years and the involuntary movements evolve to dystonia in the later stages of the illness. Walking becomes more and more associated with falls and eventually, the person is wheelchair or bed bound. Tone increases with disease progression. There is commonly a dramatic, reflexive increase in tone when the limb is activated. Reflexes are hyperactive. The Babinski often becomes positive.

In contrast to the major motor findings, sensory abnormalities are minimal or absent. Some believe that patients with advanced HD have decreased pain sensation.

Cognition

Many of the early studies reported general intellectual and cognitive decline in HD, which is worse than other neurodegenerative conditions. However, intellectual ability generally remains stable over time, with the most pronounced deficits seen in executive domains in parallel with pathological changes. Zakzanis, in a meta-analysis of the literature, which incorporated the results from 760 patients, noted that maximum differences between controls and HD patients, using the effect size statistic, were found on tests of construction, and memory.

Snowden et al. reported the results of a longitudinal follow-up of 87 HD patients recorded over 3 years. Their sample ranged in disease severity from severe to mild on the Shoulsan and Fahn Scale. At 1 year follow-up, large effects were noted for executive and memory tasks; particularly, verbal fluency, the Stroop test, and object recall. The Motor Impairment Scale of the UHDRS contributed to change on the Stroop and object recall. Illness duration made only a minor contribution to change on object recall. CAG repeat, age, and sex did not contribute to change. At 3 year follow-up, a similar pattern of scores was obtained. Speed-based tasks and memory changed significantly over time. The observed impairment was thought to relate to a primary impairment in executive functioning, which impacted on encoding and retrieval.

Thus, many studies of cognitive functioning in HD report generalized decline in cognitive functioning over the course of the condition. However, the specific nature of this decline varies between studies. It is likely that this reflects an inherent variation in the presentation of the disease within and between families, as well as poor study design and differing measures. In particular, because of the relative rarity of the disease, many studies are insufficiently powered with respect to patient numbers.

Language Ability

Traditionally, HD patients do not present with clear cortical aphasia. However, as more sophisticated testing has emerged, it has become clear that many patients presented with a range of language-based functions, some of which are masked by the severity of dysarthria. Comprehension is generally thought to be intact. However, HD patients have been shown to be impaired in the comprehension of affective and propositional (command or question) prosody.

Executive Functions

Recently, there has been increased interest in the executive deficits experienced by patients with HD. This not only results from the earlier application of more sophisticated diagnostic testing that enables patients to complete tests sooner in the course of the disease, but also reflects the improved resolution of current neuroimaging techniques. Such techniques have facilitated a greater description of the nature of the lesions in HD and identified degeneration in the frontal lobes via fronto-striatal connections. That is, the nature of the reciprocal connections between the basal ganglia and the oculomotor region, dorsolateral prefrontal cortex and lateral orbitofrontal area result in significant degeneration in fronto-striatal mediated cognitive and behavioral functions.

HD patients have been shown to be impaired on tests of planning, self-order working memory, and tests of response set, all indicators of executive dysfunction. Rosser and Hodges reported that patients with HD and Alzheimer's disease were impaired on letter and category fluency tasks. However, HD patients appeared to find letter (phonological) fluency harder than category (semantic) fluency. This was the opposite pattern to patients with Alzheimer's disease.

In summary, patients with HD show deficits on a range of tests of executive function. These take the form of planning, executing, and inhibiting behavior. In the context of the neuropathological data, it is not surprising that HD patients should present with such difficulties. Loss of frontal white matter and neuronal cell loss have been reported in many studies and metabolic deficits in the frontal lobes have been associated with the degree of cell loss in the basal ganglia.

Attentional and Perceptual Functions in HD

In many studies, HD patients were found to be impaired on tests of alertness, divided attention, and response flexibility. While clear disorders of perception are rare, there has been increasing interest and controversy surrounding the issue of patient's ability to perceive emotional cues. HD patients were impaired at interpreting facial and vocal expressions of emotion, and similarly, those relating to fear and disgust were disproportionately impaired. HD patients have also been shown to be impaired at comprehending emotional prosody in speech, matching facial affect, facial recognition, and discriminating faces.

These deficits suggest that patients have difficulty perceiving their environment, interpreting and identifying the expressions of others, and perceiving their own physical symptoms.

Memory

There has been a great deal of debate concerning the nature of the memory impairment in HD and the pattern of impaired and preserved skills in this patient group. It has been clear for many years that patients present with a form of memory impairment that, while severe, is distinct from other dementias such as Alzheimer's disease.

Global memory deficits are common in HD and this is unsurprising given the links between the striatum and limbic system, the reported deficits in temporal lobe function, and

the deficits in frontal function in this population. Unlike Alzheimer's patients where episodic memory is better for older memories, HD patients show no advantage for older memories over more recent ones. This is known as a flat temporal gradient. Procedural learning is also impaired. In particular, procedural motor tasks are more impaired than lexical tasks. It has been suggested that recognition memory is disproportionately preserved until later stages and therefore, retrieval or encoding deficit are favored by many authors. That is, the memory impairment in HD, which begins early in the course of the disease, is related to the more extensive and global deterioration in fronto-striatal functions.

Neuropsychiatric and Behavioral Features

Depression is very common in HD. Emotional dyscontrol with outbursts of anger with a physical component can be a major source of upset in the family or in the long-term care facility. Obsessive compulsive behaviors are also common. Some have paranoid delusions but hallucinations are rare. These behaviors can lead to antisocial acts that run afoul of the law. Over time, persons with HD become more and more restricted mentally. In early stages of illness, they perform cognitive tests more slowly. By history, they are less active mentally and can display prominent apathy. In general, patients with Huntington's disease don't completely lose one specific cognitive domain but rather lose the ability to engage these domains for goal-directed behavior. Communication can be especially difficult in the later stages. This can also be a source of tremendous frustration when the patient's primal needs are not met and communication is not possible to resolve these needs. As an example, it is not unusual for patients in the later stages to become anxious and upset when hungry but not able to transmit the fact that they are hungry to their caretakers.

Behavioral Difficulties

The behavioral features of HD can be conceptualized as frontal disconnection syndromes. The earliest changes can be seen as irritability with a low tolerance of frustration. These features gradually deteriorate and the episodes can become increasingly explosive and disproportionate. These features resemble the personality conditions often associated with frontal lobe impairment such as the pseudopsychopathic and the pseudodepressive states of apathy and self-neglect. Agitation and aggression can often occur in the latter stages of the disease and are often difficult to ameliorate. Up to 40% of patients suffer from affective disorders with hypomania and mania seen in 5–10%. These may occur before any signs of the disease are apparent. These underlying organic symptoms do also coexist with the psychological reaction to living with such a devastating condition. The risk of suicide is increased in HD as a result, and up to 6% of patients will die by suicide.

Managing psychiatric symptoms is difficult and is exacerbated by the cognitive and physical disabilities. A marked loss of insight early in the disease might appear protective at times but can also hamper attempts to manage symptomatology. Pharmacological treatment has been widely discussed and is usually symptomatic management.

Family and Psychosocial Issues

There are, understandably, significant family stressors and there are marked difficulties for both affected and unaffected siblings. The suicidal rates are higher in unaffected siblings, so-called survivor guilt than the general population. Similarly, unaffected parents suffer the difficulties of caring for spouses and affected children with economic and psychological difficulties. Significant support is needed for HD families from the multidisciplinary team.

Care and Disability Management of the Person with the Huntington's Mutation

The offspring of persons with Huntington's disease have a 50% chance of inheriting the disease. The penetrance is high. Though there can be variability, most develop signs at about the same age as their parents did. The genetic test for the huntingtin mutation is clinically available from analysis of blood DNA. The decision to be tested is a very personal one and needs to be supported with appropriate genetic counselling. The first reaction of many at-risk persons is to jump at the chance of being tested to "get rid" of the fear of whether they have inherited the "bad gene." However, those that do not have the mutation do not face the tragedy of the illness, and those that have inherited it can have their fears substantially enhanced by a "positive" test. Key to the counselling process is to ensure that the at-risk individual has a sense of how it will be helpful for them to know that they will get the disease in the future. Decisions surrounding whether to have children generally predominate in presymptomatic testing but, as might be expected, many choose not to be tested. Most agree that children should not be tested.

As symptoms of HD develop in a person at risk, the diagnosis is made when the physician is convinced by the chorea or some other neurological sign. Gene testing may be helpful if there is a need for the diagnosis and the signs are equivocal. It may be helpful in cases in which there is no family history, though the implications of genetic testing need to be planned for including the discovery of nonpaternity, or the establishment of risk within a larger family. Other diagnostic tests are not necessary in the clear-cut case of HD though the MRI shows progressive atrophy of the caudate throughout the course of the disease.

In the early stage of Huntington's disease, as well as in the later stages, the psychiatric manifestations require management. Depression in HD can respond to antidepressant medication but the response is often partial. Obsessive compulsive behaviors can be very difficult to control but may respond to serotonin-uptake inhibitors that are effective in the treatment of OCD. Sleep disorders are common and sleep studies show that awakenings from sleep are often associated with an involuntary movement. Some develop completely reversed sleep–wake cycles, remaining awake at night and sleeping much of the day. Longer acting benzodiazepines such as clonazepam at bedtime can improve sleep.

Mood disorders with frequent episodes of emotional upset can respond to mood stabilizers such as valproic acid, carbamazepine, and serotonin-uptake inhibitors. Antipsychotics are sometimes necessary in persons with delusions and are often tried in persons with disruptive, self-injurious, or violent behaviors. Atypical antipsychotics such as quetiapine

may be more effective than standard neuroleptics and they also do not contribute to dystonia and motor dyscontrol to the same extent. Some seem to respond to high doses of beta blockers. Because these medications are generally not as beneficial as one might hope and they are fraught with side effects, it is important to attempt to determine if there are environmental contributors to the disruptive behaviors.

Changes in mealtimes, discomfort in the wheel chair, misinterpretation of the caregiver, nicotine withdrawal, interruption when drowsy, etc. can be the source of behavioral disturbance.

There is no treatment for the motor dyscontrol though a novel "dopamine stabilizer," ACR16, has shown promise in an initial clinical trial. Replication studies are underway by the company, NeuroSearch. Speech and swallowing therapy may help teach safe swallowing. Physical activity to maintain muscle tone may be helpful. Chorea will respond to low doses of neuroleptics or to tetrabenazine, though it is important to check whether the drugs are associated with better overall motor function due to the bradykinesia and dystonic side effects. Often, the environment needs to be modified. Padding wheel chairs and bed rails, to avoid trauma from the chorea, may be critically important. Abnormal movements may be so severe that the patient is not safe in a bed and better cared for on a large mattress that rests on the floor. Use of restraints is especially problematic as, combined with the choric movements, the restraint ties can lead to significant harm, even strangulation.

Feeding the person with advanced HD is also challenging. Oral feedings need to be changed over time to a softer but thick consistency. Early on, thin liquids like water and dry crumbly foods cause cough and aspiration. Then, solid foods are too difficult to chew and swallow. One characteristic of persons with HD is that they tend to overstuff the mouth as their swallowing efficiency decreases and swallowing takes more and more time. Caregivers may continue oral feeding into the late stages with pureed foods but feeding is done very slowly over long time periods. Weight management is important as patients with HD tend to deteriorate with weight loss and, in some cases, have improved with weight gain. The decision to insert a feeding tube is especially difficult and needs to be discussed with the patient or family years before the decision is anticipated. Otherwise, the patient may be unable to communicate when the feeding crisis occurs. In general, patients with HD die of aspiration pneumonia, so a feeding tube can prolong life for those who are very severely disabled.

Pathogenesis of HD

The discovery of the Huntington's disease mutation raised the expectations that a treatment to slow progression of disease might come from research. At phenotypic level, research continues to investigate the manifestation of cognitive and behavioral impairments in HD. In particular, it is important to examine variations in the phenotype with age and CAG repeat length as well as investigations of the influence of fronto-striatal executive dysfunction on other cognitive domains.

Genetic animal models of the disease in flies, rodents, sheep, and nonhuman primates are now available or are soon to be available for therapeutic research. The normal huntingtin

protein is found throughout the cytoplasm of all cells in the body. The mutated huntingtin protein forms abnormal aggregates in neurons. A number of other CAG repeat neurodegenerative disorders have been discovered in which the abnormally long glutamine repeat is found in different proteins. All are characterized by aggregation of the abnormal protein in neurons. In patients with Huntington's disease (except the very rare person who is homozygous for the mutation), there is one normal copy of the gene and one mutated copy. It is now known that one normal copy is sufficient for normal brain function, so the disease is caused by some abnormal toxic effect(s) of the protein due to the elongated glutamine repeat. A variety of theories of pathogenesis are supported by variable levels of evidence and some therapeutic agents are now being tested in patients. The huntingtin protein has been implicated in a host of important cellular functions and the exact mechanism by which the mutation causes cell death is not clear. Mutant huntingtin affects the transcription of different classes of other genes. It interacts with proteins important in vesicular trafficking, intracellular transport, mitochondrial and synaptic function. Experiments have also shown that expression of the mutant protein, even if confined to glia, is still toxic to neurons.

Development of Neuroprotective Therapies

At present, there is no medical treatment that is known to affect the rate of progression of HD. The one possible exception is the maintenance of caloric requirements, as weight loss has been associated with more rapid deterioration. The goal of scientists is to develop a neuroprotective therapy that can be used safely in persons who are gene positive to prevent the onset of disability. The National Institute of Neurological Disorders and Stroke is currently funding a large trial of coenzyme Q10 to slow progression of HD in symptomatic patients. A prior trial of Coenzyme Q10 failed to demonstrate a large effect but there was a trend toward benefit that warranted a second study of higher dose. Among its putative actions, Coenzyme Q10 is important in mitochondrial function and there is some evidence of mitochondrial dysfunction in HD. In another attempt to improve energy metabolism, creatine supplementation is also being studied in an NIH-funded trial. Phosphocreatine is a major source of stored energy in the brain.

A major focus of research is on how best to "turn off" the mutant huntingtin gene. Recent research has shown that complete loss of the huntingtin protein is embryonically lethal suggesting that complete "turn off" of both alleles would be dangerous. The discovery that short strands of RNA can attach to messenger RNA and prevent transcription of protein raises the possibility that such interference RNA (iRNA) can be engineered to stop the production of the mutant protein. Whether iRNA treatment would be beneficial if it "turns down" expression of both the mutant and the normal allele is not clear. If not, then an allele-specific iRNA may be custom engineered for individual families so that it interacts with only the mutant gene. Antisense RNA therapy is also being pursued with similar aims. The challenge facing human use of these exciting therapies is how to deliver to the brain without adverse effects.

A variety of efforts are now ongoing to understand how to clear the protein aggregates from neurons, which seem to be the signature feature of most neurodegenerative diseases.

To that end, techniques are being developed to introduce key components of antibodies into cells, called intrabodies. These are designed to attach to and promote clearance of abnormally deposited proteins like mutant huntingtin. Drugs, which promote the metabolism of protein deposits, may also prove beneficial. There are now attempts to use high-throughput screening techniques to find drugs that prevent the aggregation or decrease production of the huntingtin protein. The mutant huntingtin protein also has been shown to alter the transcription of a variety of other genes. The downregulation of brain-derived neurotrophic factor (BDNF) is one example of an important consequence of the effect of huntingtin on gene transcription. Drugs, which modify gene transcription, particularly histone deacetylase (HDAC) inhibitors are under study as potential therapeutic agents.

Conclusions

Huntington's disease is a progressive neurodegenerative disease for which there is currently no cure. However, despite this, there is a wealth of information available to provide evidence-based efficacious treatments for the management of the patient's condition. Patients present with a triad of cognitive, movement, and psychiatric difficulties, which progress slowly over a 15–20 year period. Each of these domains requires careful assessment and management in order to maintain the person's quality of life and functional ability. Extensive advances have been made in the understanding of the pathophysiology of the condition but further care is required if services are to avoid a nihilistic approach to HD.

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