

# Huntington's disease: clinical and aetiologic aspects

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## Summary

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Huntington's disease is the most prevalent inherited human neurodegenerative disorder worldwide, affecting between 2 to 8 per 100 000 inhabitants of Western countries, with an average age of onset close to 40 (range 2–80) and a usually slow progression over 10 to 30 years. Tremendous progress has been made in the understanding of the mechanisms implicated in this disease since the original description by George Huntington in 1872, marked by the identification of the locus in 1983 and the responsible gene in 1993. Clinical features include impaired motor control, manifesting as motor impersistence and inability to perform tasks that require motor sequences, along with abnormal movements such as chorea, athetosis, impaired ocular saccades and characteristic gait disturbances. Psychiatric and cognitive symptoms are also prominent, including depression and psychosis, with a high incidence of suicide, personality changes, aggressive or uncontrolled behaviour, impaired problem-solving abilities and ultimately more diffuse neuropsychological deficits leading to dementia. Genetically, the disease demonstrates fully penetrant autosomal dominant inheritance through a CAG trinucleotide repeat expansion in the protein-coding region of the *huntingtin* gene. There is an inverse correlation between the number of repeats and the patient's age at onset of the disease. Due to a phenomenon referred to as *anticipation*, the number of CAG trinucleotide repeats tends to increase when the disease is inherited from the father (paternal transmission),

with disease onset at a younger age in the affected children. Despite 10 years of intensive study, the exact route between mutant protein and neurodegenerative illness remains elusive. Protein aggregation, mitochondrial dysfunction, transcriptional dysregulation, calcium homeostasis and signalling abnormalities, and organellar transport defects are leading candidate disease mechanisms. Huntington's disease pathology is characterised by marked atrophy of the caudate and putamen, with involvement of cerebral cortex, thalamus, subthalamus, nucleus accumbens, globus pallidus and substantia nigra pars reticulata. Within the caudate and putamen, the medium spiny GABA-ergic projection neurons are selectively vulnerable. Huntington's disease progresses slowly but irremediably to a state where patients are bedridden and demented, followed by death from secondary complications such as pneumonia. Current disease treatment is limited to pharmacologic management of symptoms, mostly antipsychotics, both for the abnormal movements and some psychiatric symptoms, and antidepressants. Future therapies targeting underlying disease mechanisms are currently under evaluation, raising tremendous hope for the development of curative treatments. They include metabolic support, neurotrophic intervention, cell replacement, transcriptional regulation and reducing the expression of the causative gene using small interfering RNA.

**Keywords:** Huntington's disease; chorea; genetics; CAG repeat

## Introduction

In 1872 George Huntington described a “hereditary chorea ... confined to certain and fortunately few families, ... [with] three marked peculiarities ...: its hereditary nature, a tendency to insanity and suicide, [and] its manifesting itself as a grave disease only in adult life” [1]. Since then, tremendous progress has been made in the understanding of the transmission and pathogenesis of this disease, with localisation of the gene in 1983 [2],

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followed by the description of the pathogenic mutation in 1993 [3]. Huntington's disease is a fully penetrant autosomal dominantly inherited progressive neurodegenerative disease, characterised clinically by abnormal movements, impaired motor and emotional control, and cognitive decline. New mutations are extremely rare. Prevalence in the general western population is reported to be 2 to 8 per 100 000. The mean age of onset is between 35 and 40, but patients have been described to present with initial symptoms from 2 to 80 years of age. Disease duration is usually between 10 to 30 years, until death occurs due to secondary causes, such as pneumonia.

This article will outline the major clinical aspects of Huntington's disease, recent insights into its pathogenic mechanisms and future prospects for therapy.

## Clinical manifestations

### Motor symptoms

The core feature of Huntington's disease is chorea (from the Greek "to dance"), comprising rapid, fluid and semi-purposeful involuntary movements involving virtually any part of the body, manifesting as facial grimacing, eyelid elevation, head bobbing, and writhing and jerking of the limbs. In early stages of disease these movements are well incorporated into normal motor activity, typically with conversion of an involuntary movement into a seemingly voluntary one (parakinesia), but over several years they become more and more visible and start to interfere with daily activities. Often, slower distal athetoid movements coexist. Motor control is altered, with impersistence and inability to perform tasks involving motor sequences, ultimately leading to severe impairment of voluntary movement. Previously thought to be a late manifestation, eye movement abnormalities, mostly difficulty in generating voluntary saccades, are now known to be an early sign of the disease [4]. Other eye movement abnormalities include increased latency of response, non-suppressible eye blinks or head movements associated with saccades and reduced saccade velocity. Consistent with the origin of the term chorea, Huntington's disease gait has a characteristic dance-like aspect, the patient appearing to be thrown off balance by involuntary movements and moving in a zig-zag pattern.

Approximately 5 to 10% of the patients present with juvenile Huntington's disease (defined as onset before age 20, also called the Westphal variant), in which rigidity, dystonia and action

tremor are often the primary manifestations, sometimes accompanied by cerebellar signs and seizures.

In a cross-sectional analysis of 45 Venezuelan Huntington's disease patients, chorea, dysdiadochokinesia and oculomotor abnormalities were all present in early stages of the disease, worsening in concert thereafter, while rigidity and dystonia increased in later stages [5]. Among subjects first rated to be disease-free and who subsequently developed Huntington's disease after more than 5 years, slowing of rapid alternating movements or abnormal saccadic generation at first evaluation was a highly sensitive (84%) and specific (69%) predictor of Huntington's disease development.

As the disease progresses, bradykinesia, dystonia and gait difficulties worsen, and patients eventually become bedridden. Associated abnormal movements may appear, including myoclonus, tics, bruxism and ataxia. Hypertonicity bears both pyramidal (spastic) and extrapyramidal (rigid) components. Dysarthria is a prominent feature, often associated with dysphagia, which leads to weight loss and infection.

### Psychiatric and cognitive symptoms

In the early stages of Huntington's disease, subjects frequently experience impaired problem-solving abilities, difficulties with visuospatial skills and attention disorders, which can lead to a decline in performance at work. Personality changes often occur in early stages and may be associated with depression, which is the most frequent psychiatric disorder, affecting up to 50% of patients. The incidence of suicide is high in Huntington's disease patients as well as Huntington's disease at-risk relatives [6.] Other psychiatric features include mood instability, outbursts of rage, psychosis, paranoia, anxiety, irritability, mania or obsessive behaviour. Apathy is a frequent complaint. With disease progression cognitive impairment worsens and leads to dementia [7].

## From gene to disease

### Genotype-disease presentation relationships

The gene locus involved in Huntington's disease was one of the first human disease loci to be chromosomally mapped (to chromosome 4 [2]). The nature of the mutation, discovered in 1993, is a variable trinucleotide (CAG) repeat expansion in exon 1 of the gene now known as *huntingtin*

(also *HD, IT15*). This type of mutation is common across a class of neurodegenerative disorders, collectively known as polyglutamine (polyQ) diseases because the trinucleotide repeat encodes an expanded stretch of glutamines in their corresponding proteins. In Huntington's disease a normal benign *huntingtin* allele carries 34 or fewer CAG repeats, whereas an allele with 35 repeats or higher predisposes to disease and alleles carrying 40 or more repeats are fully penetrant. Above the disease-causing threshold, age of Huntington's disease onset is inversely correlated with CAG repeat length. The careful study of heterozygous Huntington's disease mutation carriers in 83 kindreds of a Venezuelan Huntington's disease cohort confirmed the major effect of CAG repeat length on disease onset (accounting for 72% of the variance in age of onset overall), but further clarified that among the majority of Huntington's disease cases (with repeat lengths of 40–58) repeat length accounts for only 44% of this variance [8]. In the entire set of Venezuela kindreds residual variance in onset (not attributable to CAG repeat length) was estimated to be approximately 37% genetic and approximately 63% environmental (shared and unshared) [8]. *Htt* alleles carrying 60 or more repeats invariably result in juvenile-onset Huntington's disease (see "Clinical manifestations") and 60 is also the mean CAG repeat size in this patient group. Juvenile-onset disease is more frequently inherited paternally than maternally, presumably due to a higher probability of repeat expansion through spermatogenesis. Such inheritance is thus manifest as *anticipation*, where the child's disease has an earlier onset than that of the disease-gene-carrying parent.

#### The huntingtin protein and its mechanisms of toxicity

The discovery of the Huntington's disease gene was an important breakthrough, and it was anticipated that the elucidation of the huntingtin protein's primary structure would bring rapid insight into the molecular and cellular mechanisms underlying the disease. Despite the creation of many useful genetic Huntington's disease models [9, 10], however, the path toward a clear understanding of this process has remained slow and arduous. Elucidating mutant huntingtin's neurotoxic effects may be difficult due to the protein's particularly large size ( $\geq 3144$  amino acids,  $\geq 350$  kDa) and apparent multifunctionality. Huntingtin has been reported to interact with membrane lipids [11] and a large number of proteins [12, 13]. In some cases

the mutant protein shows a differential affinity in its molecular or organellar interaction compared to its wild-type counterpart, and these differences have been implicated in the disease process. In addition, mutant huntingtin-driven protein aggregation may be an important disease mechanism.

It has been suggested that polyglutamine disease-related neurodegeneration results primarily from a gain of function in the mutant protein. Theoretical and experimental evidence have generally supported the hypothesis that disease-causing polyglutamine proteins are abnormally prone to adopt beta sheet conformations, to self-associate and to form large assemblies that recruit other proteins [14, 15]. These abnormal and potentially toxic protein complexes have been described as aggregates or inclusions, the latter term referring to structures that can be observed by light microscopy. The nature of the exact molecular species which cause(s) neurotoxicity has been a topic of intense study and debate. This subject has come to the forefront because it is hoped that future therapeutic interventions can target the toxic species specifically by preventing its formation, promoting its elimination or converting it into a non-toxic form.

Although Huntington's disease is caused by a single mutant protein, Huntington's disease pathogenesis appears to be complex. The multipartite effects of mutant huntingtin are probably due to its widespread distribution in the cell. Mutant huntingtin appears to sensitise neurons to excitotoxicity through interaction with glutamate receptor complexes at the plasma membrane [16], association with calcium-regulating inositol triphosphate receptors in the endoplasmic reticulum [17], interfering with mitochondrial calcium dynamics [18]. Systemic administration of succinate dehydrogenase inhibitors, which act on both complex II of the mitochondrial electron transport chain (ETC) and the tricarboxylic acid cycle (TCA), mimic Huntington's disease pathology. ETC and TCA cycle abnormalities, which are also seen in human Huntington's disease brains, are likely to impair many energy-dependent cellular pathways and contribute to oxidative stress.

Characteristic changes in gene expression have been observed in both human Huntington's disease and Huntington's disease model systems [19, 20]. This effect is attributed to transcriptional dysregulation through aberrant interactions between huntingtin and various transcriptional regulators, which may occur through soluble protein binding or the sequestration of these factors into polyglutamine inclusions.

Inhibition of organellar transport also appears to contribute to the pathogenesis of Huntington's disease. Whereas normal huntingtin positively regulates the neuritic transport of organelles, such as vesicles containing brain-derived neurotrophic factor (BDNF), the presence of mutant huntingtin inhibits this process [21]. It is also likely that intracellular inclusions block organellar movement through axons or dendrites.

### Presymptomatic and symptomatic testing

Genetic testing is now widely available for Huntington's disease, as well as for several other trinucleotide repeat diseases. Such testing should only be done after the ethical and social implications of the result are considered carefully, first acknowledging the fact that having one family member test positive immediately reveals that many others are at high risk (see Cina and Fellmann, in this issue). Ethical issues also include who has a right to be tested, who has a right to the information and what the tested individual will do with the result – positive or negative. Appropriate genetic counselling and neurological and psychiatric evaluations are required in order to help the individual deal with the possible result of the test.

### Pathological and imaging findings

Atrophy and gliosis of the caudate nucleus and the putamen are the pathological hallmarks of Huntington's disease [22], although abnormalities exist in the cortex, thalamus, subthalamus, nucleus accumbens, globus pallidus and substantia nigra pars reticulata. In the caudate and the putamen, there is massive loss of GABA-producing medium spiny neurons projecting to the external globus pallidus, with relative sparing of the large aspiny striatal interneurons. These cells contain intraneuronal inclusions, with mutant huntingtin protein and  $\alpha$ -synuclein [23]. Glucose uptake is reduced in the caudate and putamen of Huntington's disease patients and can be measured by 18F-2-deoxy-D-glucose PET scan [24]. Morphometric MRI imaging shows a progressive atrophy of the caudate and putamen which becomes statistically significant approximately 11 or 9 years prior to disease onset, respectively [25]. Heterogeneous cortical thinning is also observed by MRI in individuals with preclinical Huntington's disease, and its spatial distribution pattern correlates with specific neuropsychologic measures (symbol digit,

stroop, verbal fluency) [26]. Whole brain atrophy has also been detected in longitudinal measures of early-stage Huntington's disease patients over periods as short as 6 months [27].

### Treatments

#### Symptomatic treatments

The mainstay treatment for severe chorea has historically been typical anti-psychotics like haloperidol, but atypical agents (e.g. clozapine, quetiapine) are now preferred because of their fewer extrapyramidal side effects. The potent presynaptic anti-dopaminergic tetrabenazine is very effective in reducing chorea, but parkinsonism and depression limit its usage. Depression responds well to standard SSRI therapy. Atypical anti-psychotics are useful for managing psychosis, paranoia and/or aggressive behaviour.

#### Surgical, neuroprotective and other currently experimental strategies

The development of surgical interventions for Huntington's disease has focused on foetal tissue transplant strategies [28], which have shown evidence of improvement in cognitive and motor symptoms [29]. However, confirmation of benefit awaits the results of larger ongoing trials.

Coenzyme Q10, an antioxidant and cofactor involved in the mitochondrial electron transfer chain, showed modestly encouraging results with functional decline slowing after 30 months in a randomised controlled trial [30]. Minocycline, a tetracycline antibiotic, has also been shown to have anti-apoptotic, antioxidant and anti-excitotoxic effects in Huntington's disease model systems [31]. In a small open-label clinical trial it also showed a beneficial effect in Huntington's disease patients [32]. The potential benefit of high doses of the nutritional supplement creatine is currently being studied, based on favourable outcome in animal studies, yet negative results have been reported in a 1-year randomised controlled trial with lower doses [33].

Histone deacetylase inhibitors, which may reverse transcriptional abnormalities [34, 35], are currently in clinical trials. Given evidence for deficits of both BDNF gene transcription [36] and the axonal transport of BDNF-containing vesicles in model systems [21], and the known importance of BDNF in the differentiation and survival of the striatal medium-spiny neurons that degenerate in

Huntington's disease, this trophic factor is also an interesting therapeutic candidate.

As mentioned above, the structural understanding and targeting of mutant protein aggregates has a strong rational basis [15], but these studies are still in an early phase. Complementary approaches to limit the accumulation of toxic protein species have also been proposed. These are the stimulation of autophagy [37] and the inhibition of proteases such as calpains and caspases that may generate huntingtin fragments with an increased potential to aggregate [38, 39].

Recent breakthroughs in several scientific disciplines have resulted in a new approach to inhibit the expression of mutant huntingtin at the level of its RNA transcript. The administration of newly introduced nucleotide sequence-specific small interfering RNAs to genetic Huntington's disease models has yielded impressive functional improvements [40]. Clinical implementation of siRNA therapy requires optimisation of delivery, dosage and timing, however. Also, questions of allele-specific silencing and side effects remain to be addressed. Despite these potential obstacles, RNA interference nonetheless remains a promising therapeutic strategy. If proven feasible, siRNA therapies could be effective in a considerable number of polyglutamine and other disorders where preventing the accumulation of a toxic gene product could avert or greatly diminish pathogenesis.

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