Huntington's disease: Neuropsychiatric manifestations of Huntington's disease

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Abstract

Objectives: Huntington's disease (HD) is a profoundly incapacitating, and ultimately fatal, neurodegenerative disease. HD is presently incurable, so the current goal is to allow affected individuals to live as well as possible with the illness, to maximise functional independence and quality of life for the person with HD, their carers and family members. This clinical update review focuses on the common neuropsychiatric manifestations in HD, and outlines and evaluates the various neuropsychiatric facets of HD, including the aetiology, symptoms and diagnosis.

Conclusions: Neuropsychiatric symptoms can precede the classic motor clinical symptoms of HD (prodromal HD) by decades, and cause significant functional impairment. HD provides key insights and understanding into the organic psychiatric disorders, including contemporary clinical insights into the process of neurodegeneration and manifestation of neuropsychiatric symptoms.

Keywords: Huntington's disease, neuropsychiatric manifestations, neuropsychiatry, psychiatry

Epidemiology and historical aspects of Huntington's disease

Huntington's disease (HD) is a progressive neurodegenerative disorder usually beginning in midlife with the characteristic triad of motor, cognitive and psychiatric symptoms. Dr George Huntington first described motor dysfunction as well as the neuropsychiatric aspects of self-awareness and sexual inhibition in 1872.¹ Genetic and clinical data from the Venezuelan kindreds in the region of Lake Maracaibo represent the largest and best-characterized HD population. In these families in 1983, the unstable huntingtin gene (*IT15*) was located on the short arm of chromosome 4. In 1993, the disease was

substantiated by DNA evidence – a pathological expansion of CAG trinucleotide repeats.² The prevalence of HD varies significantly between geographical regions, with lower incidence in Asian populations. The reported prevalence of HD has increased in Western countries over the past 50 years to 9.71 per 100,000, owing to better detection, management of the disease and social inclusion.³

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Table 1. CAG repeats used in genetic testing

	CAG repeats
Normal chromosomes Individuals with these alleles will not develop HD.	≤ 26 CAG repeats (less than or equal to 26 CAG repeats)
Intermediate alleles These are associated with a normal phenotype, but unstable alleles are prone to changes during reproduction and new mutations for HD can arise from intermediate alleles, particularly with paternal transmission.	27 to 35
Zone of reduced penetrance / increased risk range The majority of people will manifest HD within their expected lifetime, but potentially with slower disease progression, less severity and at a later age. Some individuals with these CAG numbers might not develop HD. There is a risk that offspring will develop HD.	36 to 39
HD All individuals with these HD alleles will eventually develop symptoms of HD, should they live long enough.	≥ 40 CAG repeats (greater than or equal to 40 CAG repeats)
Juvenile HD A variant which typically manifests in teenage years and is associated with paternal inheritance. Behavioural symptoms and learning difficulties are often the first signs. Motor symptoms may resemble parkinsonism, and epileptic fits often occur.	>60

Note: these numbers may vary slightly between different laboratories and regions.

HD: Huntington's Disease.

Diagnosis

The mean age of diagnosis is 49 years.⁴ HD can be diagnosed on the basis of family history and motor symptoms, with progression and severity of the illness generally measured by motor deterioration and detailed neuropsychological assessment of cognition. It is listed in the Diagnostic and Statistical Manual of Mental Disorders 5 as Major or Mild Neurocognitive Disorder Due to Huntington's Disease, in the ICD-10 as HD (code G10), and new diagnostic criteria have been proposed.⁵

HD is transmitted as an autosomal-dominant trait with high penetrance.⁶ Since localisation of the HD gene, genetic testing via a highly accurate blood test is also available. A cut-off score of 40 or more CAG repeats is used to determine a positive test (those who will eventually become symptomatic with HD, should they live long enough; see Table 1). There is an inverse relationship between the length of the repeat and the age of onset, with those having longer CAG repeats having earlier onset. However, CAG repeat length does not reliably indicate the course or symptoms of illness.

Diagnostic testing can determine the nature of clinical presentation and guide treatment decisions. Specialist neurological assessment is advised as well as neuropsychological and neuroimaging assessment, as well as ensuring appropriate ongoing treatment (such as referral to a specialist clinic).

Predictive testing is also available for those at risk for HD, usually those with a family history. Standard procedure entails education, genetic counselling, psychiatric assessment if necessary and follow-up (refer to the report by Trembath et al. on 15 years of HD predictive testing in Australia⁷).

For all genetic testing, it is crucial to obtain informed consent from the patient, and also be mindful that other family members are potentially affected by the test results, with possible ramifications for employment and insurance policies. While genetic testing is a voluntary process, adverse reactions to positive results and fears about genetic discrimination are not uncommon.^{8,9} Genetic testing is also available in prenatal planning via chorionic villus sampling and amniocentesis, and in conjunction with in vitro fertilisation.¹⁰

Neuropathology and biomarker investigations

Gradual atrophy of the striatum (caudate and putamen) due to neuronal loss is the neuropathological and neuro-radiological hallmark of HD. Specific loss of medium spiny neurons in the dorsal striatum, expressing either Dopaminergic type 1 or 2 receptors, is seen as the basis for the clinical phenotype with disease progression (see Figure 1). Other neuronal loss eventuate to generalised cerebral atrophy. The exact mechanism of HD pathogenesis is currently unknown, but putative theories include

Figure 1. Clinical progression and correlates of Huntington's Disease.

Common clinical features of Huntington's Disease and their pathological correlates are demonstrated. MSN: medium spiny neurone expressing either dopaminergic receptor type 1 (D1) or 2 (D2).

Figure 2. MRI brain comparison and measurements in control person and person with Huntington's Disease.

Anatomical landmarks of the basal ganglia (putamen in blue and caudate in red) are shown on the normal T1 axial MRI (left), with measurement markers of atrophy (CC: inter-caudate distance; FH: frontal horn distance of lateral ventricles; IT: inner table of skull). In contrast, severe caudate and frontal-predominant global atrophy are demonstrated in an MRI of Huntington's Disease (right). MRI for Figure 2 is created by the authors with adapted measurements from Ho et al.¹⁴

excitotoxicity, oxidative stress, impaired energy metabolism, mitochondrial dysfunction, inflammatory events, apoptosis, autophagy, abnormal protein-protein interactions, disruption of dopamine, glutamate, cannabinoid and adenosine systems.¹¹

Brain imaging is a recommended part of diagnostic assessment. Magnetic Resonance Imaging (MRI) studies reveal characteristic atrophy of the putamen, caudate

and globus pallidus in HD patients. Frontostriatal or corticostriatal MRI atrophy (particularly caudate and putamen) have been implicated as a useful marker for disease progression.¹² Clinically, measuring inter-caudate distance against the inner aspect of the skull, or the frontal span of the lateral ventricle, are useful methods for identifying caudate atrophy (see Figure 2). Significant cerebral cortical grey and white matter loss in patients with HD is also common, particularly in frontal zones.¹³

Other investigations that are used to characterise HD but are not common in the general clinical setting include functional imaging (e.g. single-photon emission computed tomography (SPECT), positron emission tomography (PET) and functional MRI (fMRI). Recent findings in cerebrospinal fluid (CSF) studies suggest the potential utility of neurofilament light (a marker of neuronal degeneration) for determining and monitoring HD.¹⁵ Other diagnostic work-up includes serum and CSF analysis to exclude other causes of symptoms (see Table 2 for common differential diagnoses).

Clinical features of HD

There is variability in the clinical phenotype with respect to timing of onset, symptoms and progression of cognitive, motor and neuropsychiatric symptoms, and of frequent weight loss and sleep disturbances. Comprehensive batteries of self-report and objective measures have been used in several multi-site longitudinal observational studies of HD, which provide a detailed insight into the natural history of HD and measure the outcome of prospective treatments. These studies include PREDICT-HD, TRACK-HD, COHORT and the ongoing project Enroll-HD.^{16–19}

Table 2. Differential diagnoses for chorea***Hereditary/phenocopies***

Systematic disorders	Neuroacanthocytoses
	Benign hereditary chorea
	Dentatorubral-pallidoluysian atrophy (DRPLA)
	Wilson's disease
	Huntington's Disease-like syndromes type 1–3
	Neurodegeneration with brain iron accumulation
	Friedreich ataxia
	Spinocerebellar ataxia (SCA)
	Polycythaemia
	Systemic lupus erythematosus (SLE)
	Thyrotoxicosis
	Hyperglycaemia
	HIV infection/AIDS
	Paraneoplastic
	Creutzfeldt–Jakob disease
Drug-induced	Mitochondrial disease
	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
	Antiphospholipid syndrome
	Drugs (e.g. antipsychotics and recreational stimulants)
Rheumatic disorders	Oral contraception drugs
	Phenytoin
	Levo-dopa
	Chorea gravidarum
	Sydenham chorea

Motor symptoms

There may be abnormal movements or subtle clumsy and awkward movements evident early in the onset of HD, which may not be reported as symptoms. This pre-motor stage is often called the prodromal, preclinical, pre-symptomatic or asymptomatic phase, or 'preHD'. Once the classic involuntary motor symptoms and signs are evident, usually beginning with chorea, the terms symptomatic or manifest HD are used. These motor symptoms progressively worsen during the course of the disease, and cause significant difficulties for activities of daily life and function, resulting in increasing disability (see Table 3).

Cognitive symptoms of HD

The cognitive symptoms in HD primarily reflect a form of subcortical dementia characterized by memory deficits, psychomotor slowing and impairment in executive, perceptual and spatial skills.²⁰ Memory problems arise from an inefficient memory strategy for acquiring and retrieving memories rather than a primary disorder of retention, and

thus may reflect executive dysfunction. As HD advances, the ability to communicate diminishes. Common speech difficulties include dysarthria, with poor articulation and slurring of words, slow production of words, poor speech initiation and difficulty organising thoughts.

Psychiatric manifestations: the behavioural and psychological symptoms of HD (BPSHD)

Since the first description of HD, behavioural, emotional and psychiatric symptoms have been a core feature of the illness. Pre-symptomatic HD gene carriers exhibit a greater prevalence of psychiatric symptoms, particularly affective disturbances, which can precede the classical motor symptoms by up to a decade.²¹ The BPSHD have been considered the presenting symptoms of HD in up to half of all people with HD. In symptomatic HD patients, it is estimated that up to 73–98% of HD patients will have a major psychiatric disorder or psychiatric symptoms.^{22,23} Not all symptoms are experienced by all, and symptoms can wax and wane. See Table 4 for the common neuropsychiatric symptoms, including BPSHD.

Table 3. Motor symptoms of Huntington's Disease (HD)

Chorea The onset of involuntary choreiform movements in early to middle age (30s–50s) is pathognomonic of HD	<ul style="list-style-type: none"> • Typically rapid, non-purposeful and non-repetitive contractions involving the orofacial and truncal areas and the limbs worsen with anxiety and tend to be absent during sleep • May be intermittent and more obvious when the person is distracted with motor or mental tasks • More irregular, intermittent and asymmetric compared to athetosis or myoclonus • Chorea often worsens with disease progression • In advanced stages of HD, chorea may plateau or decline and rigidity and parkinsonian-like features occur more often Common manifestations include: <ul style="list-style-type: none"> • pouting, grimacing and twitching of cheeks • lifting of the eyebrows • head nodding • irregular breathing • fingers and toes flexion and extension (e.g. piano playing fingers, twitchy toes) • crossing and uncrossing of the legs • truncal restlessness
Dystonia, ataxia and bradykinesia	More common as the disease progresses Dystonia may manifest as: <ul style="list-style-type: none"> • abnormal posturing of the extremities and head • internal shoulder rotation • sustained fist clenching • knee flexion • foot inversion
Gait disturbances	<ul style="list-style-type: none"> • Ataxic wide-based gait • Impaired heel–toe walking • Increased falls
Eye movement abnormalities	<ul style="list-style-type: none"> • Pursuit • Saccade initiation and velocity

The impact of the BPSHD extends to both the person with HD and caregivers, and makes a large contribution to disease burden, lower quality of life, distress, social isolation and functional decline, often more than the motor or cognitive symptoms, and increases costs of care. However, the BPSHD are amenable to targeted intervention (both nonpharmacological and pharmacological), which can potentially delay institutionalisation and reduce associated high healthcare costs (see the second paper in this series regarding treatment).²⁴ No correlation between the presence of psychiatric symptoms and CAG repeat size has been found.²⁵ There are likely multiple causes of the BPSHD, with underlying factors including a combination of neurobiological, cognitive, psychological, social and environmental factors. Detailed knowledge of the BPSHD leads to earlier and more accurate diagnosis and appropriate management.

Advanced stage and death

HD is a progressive neurodegenerative disorder that leads to increasing amounts of disability and

dependency, ultimately leading to death. Motor symptoms of advanced HD typically include prominent bradykinesia, dystonia and rigidity, and increased muscle tone may result in joint contractures. Choreiform movements lessen but may persist in the orobuccal region and the extremities. Double incontinence can occur, and cachexia (wasting) can become manifest in advanced HD. Swallowing is severely impaired, and to prevent aspiration and the significant weight loss associated with the later stages of disease, nasogastric or percutaneous endoscopic gastrostomy (PEG) is often implemented. In the late stages, the person with HD presents with severe dementia, and is usually confined to a wheelchair or bed and reliant on high-level nursing care. Pressure sores are common due to increased immobility, but there are specialised furniture designed to lessen pressure sore risk and falls. The median survival is 24 years from diagnosis, with aspiration pneumonia the most common cause of death. Other causes include heart disease, nutritional deficiencies, skin ulcers, cardiovascular-related events and suicide (6–7%).⁴

Table 4. Common neuropsychiatric symptoms in Huntington's Disease (HD)

Symptom domain	Prevalence and disease course	Characteristics/ examples	Clinical implications and treatment	Neurobiological underpinnings
Apathy	Estimated prevalence of 34–76% Apathy has been identified as a robust predictor of pheno-conversion and disease progression, as well as closely linked to global and executive cognitive performance.		Typically manifests as indifference, reduced activity or lethargy. The symptoms of apathy can be mistaken for those of depression, as both can present with diminished interest, psychomotor retardation and lack of energy and motivation. However, apathy is more characterised by lack of motivation without the sadness, dysphoria or vegetative symptoms (e.g. insomnia, fatigue, impaired attention) of depression. To date, treatment trials for apathy in HD have been unsuccessful.	There is a moderate correlation between brain atrophy and presence of apathy. The neurobiology of apathy points towards three areas of functional connectivity: connections between the basal ganglia and the dorsolateral prefrontal cortex, orbitomedial prefrontal cortex and dorsomedial prefrontal cortex.
Depression	Depression can precede the onset of motor symptoms of HD by many years. Depression is the most common and earliest symptoms prior to the motor onset. Approximately half of people affected with HD are diagnosed with depression, and most are treated pharmacologically. The prevalence of depression varies across stages of HD. There is an initial peak of incidences in the early–middle manifest stages, followed by gradual reduction towards the later stages.		See above. Assessment may be complicated by overlap between the manifestations of apathy and depression. The identification and treatment of these comorbid conditions is important.	Gene carriers are more likely to exhibit depressive symptoms than at-risk non-carriers. The high prevalence of depression may thus be due to neurobiological vulnerability factors in gene carriers, interacting with psychological and psychosocial factors. Depressive symptoms have been correlated with increased functional connectivity and decreased structural connectivity in the default mode network and the basal ganglia.
Grieving and coping with loss	This grieving process is common in both persons with HD and their family members.		Adverse psychosocial aspects of young onset dementia may appear across disease stages; from loss of employment to the ability to self-care and live independently.	

(Continued)

Table 4. (Continued)

Symptom domain	Prevalence and disease course	Characteristics/ examples	Clinical implications and treatment	Neurobiological underpinnings
Suicide	7–10% of HD patients consider or attempt suicide. Prevalence of suicidal ideation has been found to vary at different stages of HD; for example, 9% in asymptomatic at-risk individuals, rising to 22% in the pre-diagnostic group. Two critical periods have been found for increased suicidal ideation: when individuals were informed of their proximity to onset of motor symptoms; and early symptomatic when their level of independence was increasingly compromised.		Sensitivity to the coping ability, mental state and level of support should be considered throughout the disease process. Risk factors include male gender, disease duration, phase nearing to onset, irritability, impulsivity, depression, aggression, anxiety and previous attempt. While the rationale of suicide may be related to the progressive nature of HD, some suicidal impulses arise due to cognitive impairment.	
Irritability and aggression	Irritability is common in HD, with prevalence varying from 38% to 73%. Prevalence of aggression is between 22% and 66% in the majority of studies.		Together with impulsivity, irritability can be misattributed to antisocial personality disorder. Often, substance use and psychosis may co-exist. Degree of cognitive decline, family history and motor symptoms may lessen misdiagnosis.	
Anxiety	The prevalence of anxiety in manifest HD ranges from 13% to 71%. Does not seem to be linked with measures of disease progression.		Anxiety appears to be associated with depression, suicide, irritability, quality of life, pain, illness beliefs and coping styles. Behaviours such as pacing, chanting and repetitive tapping may reflect underlying anxiety. As thought processes become less flexible, those with HD may be anxious by even small departures from routine.	

(Continued)

Table 4. (Continued)

Symptom domain	Prevalence and disease course	Characteristics/ examples	Clinical implications and treatment	Neurobiological underpinnings
Psychosis	Studies have identified rates of psychosis between 9% and 17%. Psychotic symptoms are more common early in the illness and tend to decrease with cognitive decline.		Psychotic symptoms in HD tend to be isolated and atypical, rather than schizophreniform, with persecutory delusions being the most common. Strong family history of psychosis, suicide, affective disorders and motor symptoms should prompt for further organic work-up.	The HD gene has been proposed to potentially lower the threshold for the emergence of schizophrenia.
Mania	Mania and bipolar syndromes have been found to have a prevalence of 5% to 10% in HD.		Periodic grandiosity, hyperactivity and reckless behaviour can present. Personality changes such as disinhibition, irritability and facetiousness, which resemble mania, are also common in HD, including in the premanifest.	
Disinhibition, impulsivity and other dysexecutive behaviours	Dysexecutive disorders are extremely frequent. Worsen with disease progression.		A person with HD may be perseverative or often become 'stuck' on an idea or activity. They can be rigid in their behaviour and struggle to change, adapt and/or alter routines. The degree of dysexecutive syndrome can be quantified by detailed neuropsychological assessment and strategies suggested.	The frontostriatal degeneration in HD often results in impaired inhibition and a dysexecutive syndrome.
Obsessive compulsive disorder/symptoms	Obsessive and compulsive symptoms are reported in 20–50% of HD patients. Incidence increases with greater disease severity and executive dysfunction.		Most studies in HD have identified obsessional or compulsive symptoms in patients rather than clusters of symptoms which meet diagnostic criteria for obsessive-compulsive disorder. The common obsessions reported have aggressive and contamination themes. Checking rituals were the most commonly reported. Excessive worrying and somatizations are also reported.	Neuropathological changes in the caudate nucleus and related neural circuits may underlie this increased rate of obsessive-compulsive disorder symptoms.

(Continued)

Table 4. (Continued)

Symptom domain	Prevalence and disease course	Characteristics/ examples	Clinical implications and treatment	Neurobiological underpinnings
Unawareness/ anosognosia/ loss of insight/ self-awareness	Unawareness affects up to 50% of HD patients. It is associated with reduced incidence of depression and anxiety.	People with HD may under-report the presence or severity of involuntary movements, under-estimate cognitive impairment and deny behavioural change.	People with HD may under-report the presence or severity of involuntary movements, under-estimate cognitive impairment and deny behavioural change. Negative impact on caregiver may be underestimated. Practical management of the symptom should include educating the family and screening for high-risk behaviour (e.g. driving unsafely). Recognition by clinicians is crucial because of the implications for diagnosis and optimal clinical management of HD.	Findings of an inverse relationship between insight and severity of disease suggest that cognitive impairment, in particular executive dysfunction, may be an important contributory factor.
Disturbance of the sleep-wake cycle	A range of sleep and circadian abnormalities have been reported in HD. Sleep disturbance in HD has been reported as occurring very early in the course of the disease and is temporally associated with cognitive deterioration.		Comorbid mood and sleep disorders should be addressed. Results in poorer quality of life and function and distress for the person with HD and their carers.	Hypothalamic dysfunction and disruption of circadian rhythmicity have been implicated.

Summary and conclusions

This clinical update review provides a history of HD and its diagnosis, and highlights the various neuropsychiatric facets of HD. It is important for clinicians to be aware of the high rate of psychiatric symptoms in HD, as they manifest before motor symptoms are evident (which is when HD is typically diagnosed), cause significant functional impairment and affect quality of life. There are effective management strategies, which are outlined in paper 2 of this series.²⁴

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