Huntington's disease: diagnosis and management

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ABSTRACT

Huntington's disease (HD) is an inherited neurodegenerative disease characterised by neuropsychiatric symptoms, a movement disorder (most commonly choreiform) and progressive cognitive impairment. The diagnosis is usually confirmed through identification of an increased CAG repeat length in the huntingtin gene in a patient with clinical features of the condition. Though diagnosis is usually straightforward, unusual presentations can occur, and it can be difficult to know when someone has transitioned from being an asymptomatic carrier into the disease state. This has become increasingly important recently, with several putative disease-modifying therapies entering trials. A growing number of conditions can mimic HD, including rare genetic causes, which must be considered in the event of a negative HD genetic test. Patients are best managed in specialist multidisciplinary clinics, including when considering genetic testing. Current treatments are symptomatic, and largely directed at the chorea and neurobehavioural problems, although supporting trial evidence for these is often limited.

INTRODUCTION

Huntington's disease (HD) is the most common monogenic neurodegenerative disease in the Western world, with a UK prevalence of around 5–12 per 100 000.[1] It was first described in 1872, when George Huntington reported on a hereditary choreiform disorder, with behavioural and neuropsychiatric manifestations, and almost complete penetrance.[2] Rather unusually for a monogenic neurological disease, presentation is generally in adulthood, meaning all neurologists should expect to encounter patients with HD.

It is inexorably progressive, and diagnosis can be devastating for patients and their families. It is important that they receive appropriate medical, psychological and social support, particularly when undertaking predictive or diagnostic genetic testing. There are no proven disease-modifying treatments for HD, and treatment is currently symptomatic. In this regard, evidence supporting the relative efficacy of symptomatic therapies is limited, and treatment decisions are often based more on clinician experience than trial results. Here, we discuss the clinical aspects of HD, including less common features ('*chameleons*'), the differential diagnosis, and our approach to management, which we hope will be useful to the general neurologist.

PATHOPHYSIOLOGY

HD is caused by a CAG repeat expansion in the huntingtin gene, situated on the short arm of chromosome four, and inheritance is autosomal dominant. Normal CAG repeat lengths of ≤26 are not associated with disease, while repeats of ≥36 are pathogenic (mutant huntingtin). Penetrance is incomplete with alleles of 36–39 repeats, but longer repeats convey full penetrance (table 1).[3] Approximately 6% of healthy people carry an intermediate allele (27–35 repeats). These are associated with a normal phenotype, but there is evidence that some carriers of such alleles develop manifestations of HD, presumably through somatic expansion leading to pathogenic repeat lengths in critical brain regions.[4 5] Genomic instability results in increasing CAG repeat length with successive generations, especially when inherited down the paternal line, with the clinical consequence of earlier onset and increased severity in offspring (anticipation). Alleles at the upper end of the intermediate range may, therefore, expand into the pathogenic range, particularly when paternally inherited.

The huntingtin protein is ubiquitously expressed in all animal and human cells, with high levels in the brain, although its normal function is not known with

Table 1 Clinical significance of huntingtin CAG repeat lengths

CAG repeat length	Clinical significance
≤26	Normal
27–35	Intermediate—not pathological, but may cause disease through: ► Expansion into pathogenic range in successive generations ► Genomic instability resulting in mosaicism with expansion into pathogenic range in some neuronal populations, leading to clinical features of HD in rare cases
36–39	Pathogenic with incomplete penetrance
≥40	Pathogenic with complete penetrance

HD, Huntington's disease.

certainty.[6] Mutant huntingtin is prone to aggregation, and its pathogenicity, which probably relates to the generation of toxic mutant huntingtin oligomers, occurs due to a toxic gain-of-function effect (rather than loss of wild-type function). The exact mechanisms that cause neurodegeneration remain unclear, and multiple processes have been implicated.[7] Emerging evidence suggests that huntingtin CAG repeat expansions may lead to aberrant splicing of messenger RNA encoded by exon 1, leading to expression of a toxic truncated protein.[8] While pathology occurs in multiple brain regions from early in the disease course, there is a propensity for degeneration of the GABAergic medium spiny neurones of the striatum, causing early dysregulation of the direct and indirect basal ganglia pathways.[9 10] Atrophy of the head of the caudate is typically the most striking early finding on neuroimaging (figure 1).

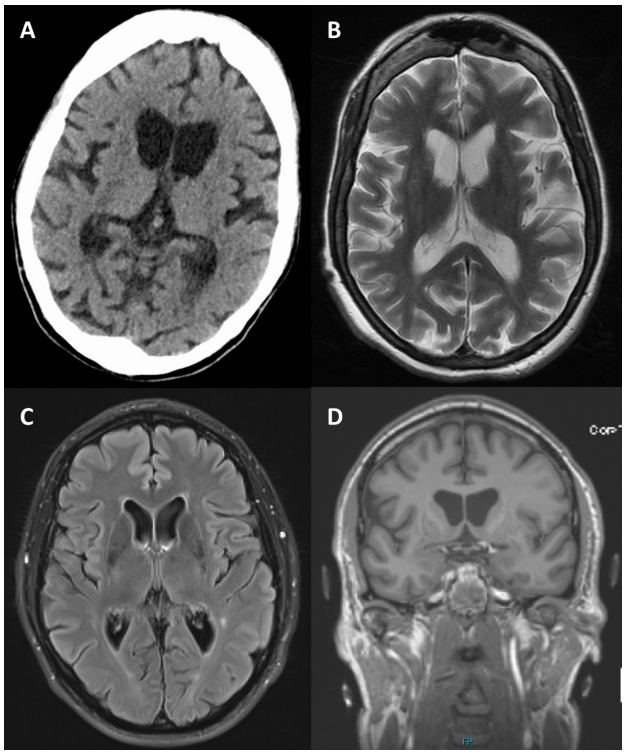

Figure 1 Neuroimaging in Huntington's disease. Caudate atrophy seen on axial CT (A) and T2 weighted (B) and fluid attenuated inversion recovery (FLAIR) (C and D) MRI sequences.

CLINICAL FEATURES

HD is characterised by the triad of neuropsychiatric symptoms, a progressive movement disorder and dementia. Though the condition may begin at any age, it passes through typical stages. Patients are generally asymptomatic for many years, before initially subtle but progressive cognitive changes occur, often with psychiatric problems. These features are followed by a movement disorder, most notably chorea. As the disease advances, the movement disorder progresses and can change from a hyperkinetic to a more hypokinetic state, with worsening cognition and mood swings. In the clinic, these features can be assessed using The Unified Huntington's Disease Rating Scale—a standardised tool consisting of motor, cognitive, behavioural and functional assessments and an independence scale.

One of the challenges in diagnosing HD is that many gene carriers who have undergone predictive testing develop symptoms without overt signs, and the question arises as to whether these are early features of HD or an overinterpretation of normal experiences and ageing, given their knowledge of their gene status. Conversely, some patients remain asymptomatic throughout most of their disease, even despite overt manifestations, owing to a poor insight (part of their condition). Thus, symptoms and signs do not always correlate in patients heterozygous for pathogenic CAG expansions, which leads to some challenges in management.

Movement disorder

The most characteristic feature of HD is the progressive choreiform movements that usually develop early in the disease course, typically in the fourth or fifth decade of life. The presence of such movements is normally used to diagnose disease onset, even though it is clear that non-motor features often occur before this point. The age at which patients present with manifest HD closely relates to the CAG repeat length, with late-onset cases having smaller repeat lengths.[11] However, at an individual level, repeat length does not reliably predict the age of onset (though repeat lengths >55 are likely to cause juvenile HD). Initially, hyperkinetic movements may be subtle (eg, fidgeting movements in the fingers when walking, or in bed at night noticed by the partner), before becoming more obvious with all body parts affected symmetrically.

Motor impersistence is another cardinal feature, whereby patients cannot maintain voluntary muscle contraction at a steady level. It may be apparent during pursuit eye movements, or when asking the patient to keep their tongue out (without clenching it between their teeth) for 10 s. Another example of this is the

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'milkmaid's grip', where the patient cannot maintain a strong handshake.

Though development of chorea is often used to diagnose the onset of manifest disease, the degree of chorea does not correlate with disease severity. In fact, as the disease advances, the chorea often plateaus and may regress, and a hypokinetic state with symmetrical Parkinsonism and dystonia can develop—a strong predictor of nursing home placement.[12] The usual presentation of juvenile HD (onset before age 21) is Parkinsonism with profound bradykinesia and dystonia, but little chorea, often with tremor and rigidity—this presentation can also occasionally occur in patients with later onset HD.

Other involuntary movements occur, including tics (sometimes difficult to disentangle from more obvious chorea), and less commonly, myoclonus, which is often stimulus-sensitive and occurs in more advanced or juvenile cases. Gait and postural stability become increasingly impaired; it is often challenging to characterise the gait disorder of HD fully, as it results from a combination of dystonia, rigidity, chorea and ataxia. All of these features predispose to falls, especially when patients enter the mild to moderate disease stages and/or develop impulsivity. Indeed, some patients with a family history can present with significant gait problems, and an ataxic syndrome with dysarthria, which may be mistaken for an autosomal dominant spinocerebellar ataxia (box 1).

Oculomotor abnormalities occur early in HD. Motor impersistence (see above) is common, as is an inability to maintain gaze, while saccadic function is frequently impaired, with patients becoming dependent on eye blinks or head thrusts to initiate saccades—features that should be sought when examining eye movements.

Finally, motor sequence movements (dependent on the integrity of the frontal lobes) are also an early casualty of the disease process. This can be demonstrated using the Luria tri-step test, in which patients are asked to perform a repetitive sequence of making a fist, then placing the medial side of the hand down, and then the palm (figure 2). Typically patients struggle to reproduce it in the correct order at a reasonable speed.

Box 1 Challenging cases from our Huntington's disease clinic

Case 1

A right-handed retired woman in her sixties had a 5-year history of progressive balance problems. Her past medical history included only mild depression. She was initially found to be ataxic and considered to have a probable late-onset genetic ataxia, though she declined genetic testing at this stage. Her MR brain scan was unremarkable.

She re-presented 5 years after her initial review with progressive gait difficulties, along with difficulties in swallowing, and dysarthria. Her son had noticed that she had developed generalised twitching movements that had been present for at least 2 years, of which she had little awareness. On further questioning, she reported that her mother had had late-onset gait and swallowing difficulty, and she had died in her eighties with no chorea, cognitive problems or behavioural issues.

On examination at this stage, she had dysarthria, motor impersistence, square-wave jerks with broken ocular pursuit, and slow saccades. There was heel–shin ataxia and a broad-based gait, and she had developed chorea in all four limbs.

Genetic testing identified a mutant huntingtin allele, with a CAG repeat length of 43.

Case 2

A teenage boy presented with deteriorating behavioural problems. He was at risk of permanent exclusion from school due to distractibility and aggressive behaviour. He had initially been diagnosed with attention-deficit hyperactivity disorder by the local paediatric team, for which he was taking methylphenidate. However, owing to his mother having a genetic diagnosis of HD, he was referred for genetic testing, with a presumed diagnosis of juvenile HD. Physical examination was unremarkable, with no chorea, bradykinesia, rigidity or eye movement abnormalities.

After extensive consultation, a genetic test confirmed that he carried an HD allele, with 51 CAG repeats. His behavioural problems were initially thought to be due to evolving juvenile HD. However, over several years of follow-up in the HD clinic, he did not develop any motor or cognitive manifestations, and it was therefore felt that he had a conduct disorder that was independent of his HD carrier status.

Neuropsychiatric manifestations

Depression and anxiety are common in HD and can be hard to distinguish from apathy, which is a pervasive aspect in most patients from an early stage. Though the movement disorder of HD may be florid, it is often the neuropsychiatric features (along with subsequent cognitive deficits), which are the most disabling features. Personality change may occur, and irritability is common. Family members may report that the patient has become increasingly intolerant and unable to control their temper, which can bring them into contact with the judicial system. Suicidal ideation is said to be frequent (including in premanifest disease), with a reported lifetime prevalence of attempted suicide of approximately 5%–10%.[13] Delusions, and less frequently hallucinations, can occur, though frank psychosis is relatively uncommon.

Cognitive deficits

Cognitive problems often begin before detectable motor features, and progress steadily.[14] The profile of cognitive problems is that of a subcortical dementia, with deficits in executive function predominating.

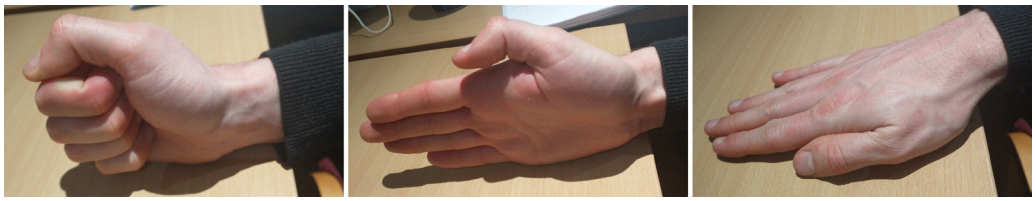

Figure 2 Luria tri-step test. The patient is asked to make a fist, then place the medial side of their hand down on the surface, and then the palm. This is repeated as many times as possible over 10 s (a normal score is completion of the sequence at least four times without cues). Patients with Huntington's disease have difficulty performing these motor sequence movements.

Learning and planning are impaired, and deficits in social cognition can result in inappropriate responses to social cues, leading to stigmatisation.[15 16] This is a particular challenge, since these features often develop at an age when patients are economically active. Another noteworthy feature is impaired mental flexibility and an inability to switch attention between different tasks.[17] Lack of insight into these deficits, combined with the development of impulsive tendencies and apathy lead to difficulties with tasks such as handling finances, and leave patients with HD vulnerable to exploitation from a variety of sources, and it is important to remain vigilant for this at review. Memory impairments for spatial information emerge early, and though language comprehension remains intact, a reduction in spontaneously generated speech is characteristic of early disease.[18 19] These deficits often lead to difficulties with relationships at home, and in remaining in employment.

Other clinical features

Weight loss is common, in part due to the high caloric demands resulting from continuous choreiform movements, but which may also have a metabolic pathology in its own right.[20] This can be aggravated by depression, apathy and dysphagia.

Most patients experience sleep problems, such as insomnia, difficulty in falling asleep and excessive daytime sleepiness. Such symptoms may exacerbate attentional deficits and affective aspects.[21] These problems occur in part due to a disturbance of normal circadian rhythm,[22] which may occur ahead of overt clinical manifestations, and may explain why many of the early non-motor features can resemble jet lag. Rapid-eye-movement sleep behaviour disorder and periodic limb movements of sleep also occur.[23 24] As Parkinsonism develops, difficulty in changing position can also disrupt sleep. It is also important to remember that some of the medications used to treat HD (eg, tetrabenazine and olanzapine), may contribute to these sleep problems.

Chameleons

Though in many cases the diagnosis of HD is straightforward owing to the characteristic clinical features and genetic nature of the condition, it can be mistaken for other diseases, and some circumstances introduce diagnostic challenge.

Young-onset disease

Juvenile HD often presents with rigidity and Parkinsonism, with little or no chorea (the Westphal variant).[25] Such patients may even present before (or have lost contact with) an affected parent, and therefore, be misdiagnosed with young-onset dystonia or Parkinsonism. Juvenile HD is also associated with seizures and major behavioural problems; if behavioural problems predominate, they may inadvertently be attributed to another cause. For example, behaviour change may be attributed to social difficulties, as the patient may be living in a household with a badly affected parent (typically the father, who is more likely to pass on an unstable huntingtin allele).[26] Similarly, behavioural abnormalities may be wrongly attributed to the presence of an expanded HD gene (box 1).

Late-onset disease

Though HD is generally a disease that presents in midlife, a late-onset of features in keeping with HD should not deter one from considering this as a potential diagnosis. Onset may occur as late as the ninth decade[27 28] and typically such patients progress less rapidly compared with younger-onset cases.[27]

Absent family history

A family history of disease is not always apparent for a variety of reasons, including parents dying young and non-paternity. It is important to consider that loss of contact with relatives may have occurred due to neuropsychiatric and behavioural features of disease in earlier generations. However, de novo cases do occur in some families, and these are likely to be explained by the expansion of intermediate length alleles into the pathogenic range. Genomic instability is more pronounced in spermatogenesis than oogenesis, so this occurrence is more likely through paternal inheritance.

Intermediate alleles

Though intermediate CAG repeat lengths in themselves are not pathogenic, they have been associated with pathologically proven HD in some cases. Their clinical significance remains a matter for debate, but

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it would seem logical to assume that they are relevant in a patient presenting with typical clinical features of HD, if other HD phenocopies have been excluded. This is hypothesised to occur due to mosaicism, with genomic instability resulting in somatic expansion of the repeat length into the pathogenic range in critical cells within the central nervous system. These alleles may be detected incidentally in individuals undergoing predictive testing, where they have been inherited from the unaffected parent, and in this situation they are likely to be clinically insignificant.

DIFFERENTIAL DIAGNOSIS AND MIMICS

In practice, the diagnosis of HD is usually straightforward, and given that HD (at least in Europe) is by far the most common inherited cause of chorea with behavioural and cognitive symptoms, the first investigative step is to test for a mutant huntingtin allele. However, if the result is negative (or intermediate), or if there are atypical features (eg, prominent seizures or rapid progression), the differential diagnosis must be considered. Even so, the cause of HD phenocopies remains undetermined in most people with a negative HD test.[29] Several genetic conditions can mimic HD (table 2), which are reviewed in detail elsewhere.[29 30]

Several genetic phenocopies closely mimic HD, and though rare, these should be considered in patients with the triad of movement disorder, neuropsychiatric manifestations and cognitive decline. Four distinct conditions have been designated to cause this HD-like (HDL) syndrome (HDL1–HDL4). These are autosomal dominant conditions that present in early adulthood to mid-adulthood, other than HDL3 which is autosomal recessive and usually presents in childhood.[29 30] HDL2 is almost exclusive to families of South African heritage, but it accounts for a significant proportion of HDL presentations in this group.[31 32] HDL4 (also called spinocerebellar ataxia 17) is more common in Caucasians, making it an important differential of HD in Europe. It is a trinucleotide repeat expansion disorder, so like HD, genetic anticipation occurs.

Many other inherited diseases may resemble HD (table 2).[29 30] Benign hereditary chorea is an autosomal dominant condition, with early onset of chorea and little or very slow progression, and symptoms may regress in adulthood.[33] Cognitive deficits are absent or mild, though learning disabilities may occur. Some mutations are associated with lung and thyroid disease, and distinguishing it from HD is important, given the significantly different prognoses. Dentatorubropallidoluysian atrophy occurs globally, but is said to be more prevalent than HD in Japan, so should be considered in patients of Japanese ancestry in particular.

Acquired causes of chorea may be considered, particularly when there is no family history (box 2). These can sometimes be distinguished from HD by the absence of motor impersistence, normal saccadic eye movements, preservation of cognition and in many cases, an abrupt onset. Tardive dyskinesia secondary to dopamine antagonist treatment is a noteworthy differential, because the psychiatric symptoms for which they are prescribed can be misconstrued as premotor features of HD. Conversely, it is important not to wrongly attribute the development of chorea in a patient with undiagnosed HD, to previous antipsychotic use. Typically tardive dyskinesia causes involuntary movements around the mouth, but can affect the trunk and limbs. Unlike HD, frontalis involvement is rare.

MANAGEMENT

Several putative disease-modifying approaches, including antisense oligonucleotide therapy, have been investigated in HD, but to date none have been shown to slow the progression of disease.[34] Thus, treatment is currently focused on controlling symptoms, psychological and social support, and improving quality of life. A set of recommendations for management of many of the symptoms of HD has recently been published, commissioned by the European Huntington's Disease Network.[35] It is important to maintain a positive approach to management, and to emphasise that although the condition cannot be cured, there are many ways in which patients can be helped.

Perhaps the most important aspect of management is the involvement of a multidisciplinary team, involving neurologists, clinical geneticists, neuropsychologists, neuropsychiatrists, dieticians, speech and language therapists, physiotherapists, occupational therapists, social workers, specialist nurses and clinic coordinators. Patient support groups (such as the HD Association in England and Wales, the HD Society of America, and the Huntington's Society of Canada) are important, and some provide funded regional advisors who work in the community with affected families. A lack of insight means that patients are sometimes reluctant to accept help, and input from family and carers can sometimes provide a better indication of the problems experienced by the patient. Discussions around advanced care planning are important before significant cognitive impairment develops, in particular with regard to determination of priorities for assisted feeding (eg, percutaneous endoscopic gastrostomy insertion), hospital admissions and care settings.

There is little evidence regarding symptomatic medications, and the choice of drug generally comes down to clinician experience. When deciding on what drug to use, it is important to consider the whole profile of symptoms experienced by the patient, because treatments used for some aspects of disease may have detrimental effects on others (eg, tetrabenazine can effectively treat chorea, but can exacerbate neuropsychiatric manifestations).

It is also as important to consider how to support the patient using non-pharmacological measures such as ensuring access to appropriate care packages, dietary

Table 2 Genetic disorders that may mimic Huntington's disease

	Gene	Typical age at onset	Suggestive clinical features
Autosomal dominant disorders			
HDL1	*PRNP*	Third and fourth decades	Seizures Truncal ataxia Quick progression (death within 10 years)
HDL2	*JPH3*	Third and fourth decades	South African ancestry Acanthocytosis Quick progression (Death within 15 years)
HDL4 (SCA17)	*TBP1*	Third to fifth decades (rare in childhood)	Cerebellar ataxia Dystonia Pyramidal features Family history of these features
C9orf72 hexanucleotide repeat expansion	*C9ORF72*	Fifth decade	Motor neurone disease/frontotemporal dementia overlap Pyramidal features Prominent early psychiatric symptoms
DRPLA	*ATN1*	Third and fourth decade	Japanese ancestry Seizures Quick progression (death within 15 years) Myoclonus prominent in juvenile cases
SCA8	*ATXN8OS*	Childhood to eighth decade	Ataxia Slow progression with normal life expectancy
Benign hereditary chorea	*TITF1*(also called *NKX2.1*)	Infancy and early childhood	Non-progressive/very slow progression Few cognitive deficits Thyroid/respiratory disease
Neuroferritinopathy	*FTL1*	Fourth to fifth decade	Orofacial dystonia Iron deposition in basal ganglia seen on MRI Low serum ferritin
ADCY5 mutations	*ADCY5*	First to second decade	Combined dystonia and myoclonus Paroxysmal chorea Worse during sleep
Recessive disorders			
HDL3	4p15.3 (gene unknown)	Childhood (3–4 years)	Autosomal recessive inheritance
Chorea-acanthocytosis	*VPS13A*	Fourth decade	Autosomal recessive inheritance Self-mutilating behaviour Acanthocytosis Peripheral neuropathy/areflexia Raised serum creatine kinase Prominent orolingual dystonia when eating Seizures
McLeod's syndrome	*XK*	Mid-adulthood Third to fifth decade	X-linked recessive inheritance Peripheral neuropathy Acanthocytosis Cardiomyopathy Skeletal myopathy and atrophy Raised serum creatine kinase Facial tics
Lesch-Nyhan syndrome	*HPRT1*	First and second decade	X-linked recessive inheritance Seizures Self-mutilating behaviour High uric acid
Wilson's disease	*ATP7B*	First and second decade	Autosomal recessive inheritance Liver dysfunction Kayser-Fleischer rings Risus sardonicus Low plasma caeruloplasmin/ raised urinary copper excretion MR brain scan showing T2 hyperintensity in putamen, globus pallidus, brainstem and cerebellum

Continued

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Table 2 Continued

	Gene	Typical age at onset	Suggestive clinical features
Ataxia with oculomotor apraxia	*APTX* (AOA1) and *SETX* (AOA2)	First and second decade	Autosomal recessive inheritance Cerebellar ataxia Peripheral neuropathy Elevated α-fetoprotein (AOA2) Hypoalbuminaemia and Hypercholesterolaemia (AOA1)
Friedreich's ataxia	*FXN*	First and second decade	Autosomal recessive inheritance Ataxia Pyramidal signs Cardiomyopathy Skeletal abnormalities Optic atrophy Deafness Diabetes mellitus Peripheral neuropathy

AOA, ataxia with oculomotor apraxia; DRPLA, dentatorubropallidoluysian atrophy; HDL, Huntington's disease-like; SCA, spinocerebellar ataxia.

supplements, and housing and benefit support. Physiotherapy and occupational therapy input can be helpful, and there is some suggestion that increased levels of activity can help to maintain function.[36] Patient support groups, such as those listed above are very important in supporting patients and their families, and patients should be directed to them. These organisations offer a wealth of information about the nature of HD, and advice about living with the condition. Many patients find attendance at local events and support groups helpful, and these offer a means of maintaining social contact for some individuals. The needs of the patient's family are not always apparent to clinicians (particularly children, who may not be present at appointments), and the patient support groups can help in addressing these. The website HD Buzz (https://en.hdbuzz.net) is an additional resource that publishes HD research news, written in plain language, which can be useful to patients and clinicians.

Box 2 Acquired causes of chorea.

Drug induced
- Tardive dyskinesia (neuroleptics).
- Levodopa/dopamine agonists.
- Anticholinergics.
- Anti-seizure medications (phenytoin, carbamazepine, gabapentin, valproate).
- Central nervous system stimulants (amphetamines, methylphenidate, cocaine).
- Oestrogens (contraceptive pill).
- Benzodiazepines.

Postinfectious/infection
- Sydenham's chorea.
- Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.
- Herpes simplex virus encephalitis.
- Subacute sclerosing panencephalitis.
- Variant Creutzfeldt-Jakob disease.

Other inflammatory/autoimmune
- Antiphospholipid antibodies/systemic lupus erythematosus.
- Coeliac disease.
- Paraneoplastic (anti-CRMP5/CV2, anti-Hu, anti-Yo, anti-NMDA-R, anti-GABA-B antibodies).

Other
- Stroke (vascular haemichorea).
- Chorea gravidarum.
- Hyperthyroidism.
- Polycythaemia vera.
- Striatal space-occupying lesions.

Genetic diagnosis and counselling

It may be appropriate for an HD genetic test to be arranged directly from the neurology clinic, but it is often advisable to involve the genetics service. A diagnosis of HD brings significant distress to the patient and family, and genetic counselling before testing is essential. All family members for which a test may have implications should be identified, and their needs considered. A positive genetic test in asymptomatic individuals that have undergone predictive testing, or in patients with poor insight into their deficits, can cause significant psychological morbidity, which must be considered when arranging genetic testing. The nature and prognosis of HD, along with the implications of a positive test on other aspects of life, such as insurance applications and occupation, should be discussed. These aspects are particularly important when asymptomatic family members come forward for testing, as they are also vulnerable to psychiatric morbidity in the event of a positive result. Predictive testing in asymptomatic individuals should only be undertaken by those with adequate expertise, and in accordance with an internationally agreed protocol.[37] Predictive testing is not performed in those under age 18. Direct testing of the fetus can be offered to pregnant individuals, but only after sufficient genetic

Table 3 Pharmacological treatment options for chorea in Huntington's disease

Drug	Starting dose	Recommended titration interval	Usual dose
Tetrabenazine	12.5 mg once daily	1–2 weeks	12.5 mg three times daily (increase to 25–50 mg three times daily as required) Maximum dose 200 mg
Olanzapine	2.5–5 mg once daily	2–4 weeks	20–30 mg daily
Sulpride (or Amisulpride)	100–200 mg two times per day	2–4 weeks	400 mg two times daily Maximum dose 1200 mg two times pdaily
Risperidone	1 mg two times per day	1–2 weeks	2–3 mg two times daily Maximum dose 8 mg two times daily
Aripiprazole	2.5–5 mg once daily	2–4 weeks	20 mg daily
Quetiapine	25 mg two times per day	1–2 weeks	200 mg two times daily Maximum 400 mg two times daily
Amantadine	100 mg once daily	1–2 weeks	200 mg two times daily
Clonazepam	0.5 mg once daily	1–2 weeks	1–2 mg two to three times daily

Drugs should be introduced at a low dose, and titrated up as required, and as tolerated. Where treatment with tetrabenazine or an antipsychotic has been ineffective or not tolerated, combination therapy can be tried.

counselling, and preimplantation genetic diagnosis is an option when carriers wish to have a family. Involvement of a clinical geneticist can facilitate decisions about such testing.

Management of movement symptoms

Chorea does not always require treatment, but where involuntary movements are causing functional or social impairment, a number of medications can help (table 3). There is little evidence about the relative efficacy of these drugs, and if one is found to be ineffective, it is reasonable to move onto another.[38]

Tetrabenazine is the only drug licensed for the treatment of chorea in HD. It inhibits the vesicular monoamine transporter 2, reducing uptake of monoamines (including dopamine) into synaptic vesicles. It should be started at a low dose (12.5 mg once daily), with dose escalation every one to 2 weeks as required. The half-life is variable, and dosing regimens therefore differ between patients (most will require two to three doses daily). There is randomised controlled trial evidence for its efficacy in reducing chorea scores, but adverse effects often limit its use.[39] These include sedation and depression, so it is most useful in patients with functional impairment due to chorea, with minimal neuropsychiatric manifestations. It is important to be vigilant for suicidal ideation (although in our experience the risk of this is low), and if this occurs the drug should be stopped. Other side effects may improve after a dose reduction.

Antipsychotic drugs are often preferred when there are comorbid behavioural issues, depression or psychosis. We find that olanzapine is a useful first-line agent, which is effective, usually well tolerated, and needs to be taken only once daily (increasing adherence). Potential side effects include sedation, dry mouth, metabolic syndrome, and weight gain (indeed, it may be preferred in part because it can help to reduce weight loss, and improve sleep and mood). Other antipsychotic agents including risperidone, haloperidol, (ami)sulpride, aripiprazole, quetiapine, pimozide and tiapride, have been reported to improve chorea, though evidence comes only from small, mostly open-label trials, and there are no large head-to-head comparisons of these treatments.[38] Where olanzapine has been ineffective or not tolerated, it is reasonable to consider another neuroleptic.

If response to tetrabenazine or a neuroleptic is inadequate, combination therapy may be considered. However, in our experience if the response to two neuroleptics and tetrabenazine has been poor then the chorea is likely to remain refractory to medication. When these drugs are used together, clinicians need heightened attention to adverse effects. It should also be noted that tetrabenazine and neuroleptics can cause extra-pyramidal side effects including Parkinsonism, which can complicate their long-term use. Amantadine may be used as an adjunct, or when the aforementioned drugs are not appropriate, though its efficacy is less clear.[40] Deep-brain stimulation of the globus pallidus has been tried for medically refractory chorea, though results have been mixed.[41] This remains an experimental treatment, with a number of trials underway. Clonazepam can be a useful adjunct in younger patients where tremor and rigidity can be problematic.

Parkinsonism may be treated with levodopa or dopamine agonists, introduced as they would be for Parkinson's disease.[42] However, we find that they rarely offer significant benefit.

Management of neuropsychological and neuropsychiatric symptoms

Cognitive and behavioural deficits including apathy, impulsivity, irritability and poor insight can result in conflict with family members and employers, and provision of an explanation for such traits through psychological assessment can be hugely beneficial. We

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Table 4 Cognitive and neuropsychiatric measures useful in the assessment of Huntington's disease

Domain	Tests
Global Cognition	► Addenbrooke's Cognitive Examination-III ► Montreal Cognitive Assessment
Executive Function	► Symbol Digit Modalities Task ► Stroop test ► CANTAB-One Touch Stockings of Cambridge
Learning and memory	► Hopkins Verbal Learning Task ► CANTAB-Paired Associates Learning
Attention	► Wisconsin Card Sorting Test ► CANTAB-IDED
Language	► Phonemic verbal fluency ► Semantic verbal fluency
Depression	► Hospital Anxiety and Depression Scale ► Beck Depression Inventory
Apathy	► Apathy Evaluation Scale
Social Cognition	► Toronto Alexithymia Scale ► Empathy Quotient ► Reading the Mind in the Eyes

therefore routinely perform neuropsychological tests to define the nature of the patient's deficits, so that these can be effectively communicated to them and their family. We routinely perform multidomain assessment, including tests of global cognition, executive function, learning and memory, attention, language, depression, apathy and social cognition (table 4).

There is no specific evidence for the use of any particular treatments for psychiatric symptoms in HD, and such problems should be treated as they would in other individuals with these disorders. Selective serotonin reuptake inhibitors (SSRIs) including citalopram and sertraline are useful for depression and anxiety, and atypical antipsychotics may be used to treat psychosis. Some patients develop marked obsessive compulsive behaviours, for which sertraline may also help.[43]

Behavioural management strategies are the priority in treating irritability, though pharmacotherapy is often necessary. SSRIs may be preferred in the context of comorbid depression and anxiety, while antipsychotics may be preferred if there is aggressive behaviour, comorbid psychosis or problematic chorea. As a general principle, the starting dose should be low, with titration every 2–4 weeks according to response. Mood-stabilising antiseizure medications (lamotrigine and sodium valproate) can be used, and tricyclic antidepressants, mirtazapine and benzodiazepines may be employed as adjuncts.[43 44]

For patients with marked sleep disturbance, education around sleep hygiene can be helpful, including the avoidance of daytime naps, taking regular physical exercise, adhering to a healthy diet, and limiting caffeine, tobacco, alcohol and screen-time before sleep. However, with disease progression, normal sleep–wake cycling tends to disintegrate. Medications should be reviewed to identify any that may exacerbate sleep issues, and the benefits and risks of each must be considered. Modafinil can be used for daytime somnolence to restore daytime alertness, which may improve sleep. Mirtazapine can help patients with depression and disordered sleep, and melatonin may help to re-establish a normal circadian rhythm, though its availability is often limited in the UK, and its efficacy unproven in HD. In some cases, Z-drugs can be helpful, and we have also resorted to sodium oxybate in some patients with poor sleep refractory to other interventions.

Driving

In the early stages of disease, patients may continue to drive, and some modify their driving habits to continue to do so safely. However, driving ability may become compromised due to impaired concentration and planning, irritability, impulsivity and motor deficits for example. Some patients decide to stop driving, often after discussion with their family, while others may be reluctant to do so due to poor insight into their symptoms. Implications for insurance and licensing must be considered, and these vary depending on disease stage and country of residence. For instance, in the UK premanifest carriers do not need to notify the driver and vehicle licensing agency (DVLA), but once overt disease is diagnosed, the DVLA must be informed.

CONCLUSION

HD is numerically the most important cause of hereditary chorea, and brings unique ethical, societal and therapeutic considerations. It most commonly presents in midlife, at a time when individuals are economically active, so though a relatively uncommon condition, it has disproportionate health and economic consequences. A diagnosis of HD has implications not only for the patient, but also their

Key points

- Huntington's disease (HD) is the most common inherited cause of chorea in the UK.
- The diagnosis of manifest HD can be difficult and brings with it many physical, psychological and social implications.
- Treatment decisions are individualised, taking into account the profile of symptoms and signs experienced by the patient, and for many therapies there is limited or no trial data supporting their use.
- Multidisciplinary management in specialist clinics focusing on psychological, social and physical support is necessary, with good links to HD patient support groups and access to their support of patients in the community.
- Several HD phenocopies may be considered in the context of chorea, neuropsychiatric and cognitive problems.

Further reading

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family, and it is important that their needs are met. Treatment decisions are largely based on clinical experience, rather than experimental evidence, and it is important that all neurologists are aware of the available management strategies.

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