Huntington's disease

Marianne J U Novak,[1 2] Sarah J Tabrizi[1 3]

[1]National Hospital for Neurology and Neurosurgery, London WC1N 3BG
[2]Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, London WC1N 3BG
[3]Department of Neurodegenerative Disease, UCL Institute of Neurology
Correspondence to: S Tabrizi
sarah.tabrizi@prion.ucl.ac.uk

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Huntington's disease is a devastating inherited neurodegenerative disease characterised by progressive motor, cognitive, and psychiatric symptoms. Patients may present with any of these symptoms, and familiarity with the phenotype is therefore important. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes before this.

The disease occurs in all racial groups but is most common in people of northern European origin. Its prevalence in the Western hemisphere is 7-10/100 000.[w1] The mean age of onset of symptoms is 40 years, but juvenile onset (<20 years) and older onset (>70 years) forms are well recognised. The Huntington's Disease Association (HDA) has records of 6161 adults with symptomatic Huntington's disease and 541 children with juvenile Huntington's disease (in England and Wales) at the time of writing. This is a conservative estimate of prevalence because it includes only those people in contact with the HDA, and it suggests that the true prevalence of the disease is higher than previously thought.[1]

Although relatively uncommon, Huntington's disease can be devastating for patients and their families. People who are at risk of developing the disease because of a family history face difficult decisions about genetic testing. We review the features of Huntington's disease, recent advances in management, and advances in the practice and ethics of genetic testing that may be relevant to a wide spectrum of health professionals.

What are the clinical features of Huntington's disease?

The disease was originally named Huntington's chorea after George Huntington, who wrote the first detailed description in 1872. More recently, however, the name has changed to Huntington's disease to reflect the fact that chorea is not the only important manifestation of the disease. Many non-motor symptoms may be more disabling and distressing than the motor symptoms.[2-4] One study assessed the effect of cognitive and motor symptoms on the ability of 67 people with early Huntington's disease to carry out activities of daily living, and found that cognitive impairment was associated with reduced functional ability independent of motor impairment.[2]

Imaging and postmortem studies have shown that the disease is characterised by cerebral atrophy.[5 6] Atrophic changes are initially seen most prominently in the striatum (part of the basal ganglia) and later become more widespread, as shown in fig 1.

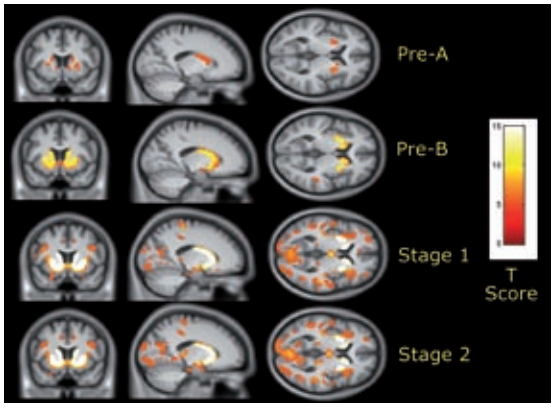

Fig 1 | Statistical parametric map showing grey matter volume loss in patient groups compared with controls. Pre-A and pre-B are premanifest Huntington's disease gene carriers with estimated time to clinical disease onset greater than and less than 10.8 years, respectively. (This was estimated using CAG repeat length and age in a formula that has been well validated and used extensively in research into Huntington's disease[w10]). Stage 1 and stage 2 are patients with early manifest disease who have no functional impairment and mild functional impairment, respectively. The figure shows progressive grey matter volume loss in the caudate and putamen (striatum) initially, followed by the cerebral cortex. Results are adjusted for age, sex, study site, and total intracranial volume and are corrected for multiple comparisons using family-wise error at P<0.05. Reproduced from Tabrizi et al,[7] with permission from the Elsevier Publishing Group

Huntington's disease progresses over 15-20 years. Characteristic symptoms reflect a triad of motor, cognitive, and psychiatric manifestations of the disease (box 1). The onset of disease is currently defined as the point at which characteristic motor signs develop[8]; this is when a patient moves from being a "premanifest gene carrier" to having "manifest" disease. This distinction is somewhat arbitrary because most patients develop cognitive or psychiatric symptoms (or both) during the prodromal ("premanifest") period, often many years before any motor signs are seen.[7 9 w2]

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SUMMARY POINTS

Huntington's disease causes motor, cognitive, and psychiatric impairment
Predictive and diagnostic genetic testing are available through specialist centres
Genetic testing for the disease has many implications for patients and families
The disease currently has no cure, but many therapeutic options exist to improve symptoms
Optimal care usually requires input from a multidisciplinary team

SOURCES AND SELECTION CRITERIA

This review is based on our experience of leading (SJT) and working in (MJUN) the multidisciplinary Huntington's disease clinic at the National Hospital for Neurology and Neurosurgery, supported by an up to date literature review performed using PubMed and a review of the Cochrane database.

Box 1 | Common symptoms of Huntington's disease

Motor symptoms
Chorea, dystonia, loss of postural reflexes, bradykinesia, rigidity

Cognitive symptoms
Disorganisation as a result of difficulties with planning, initiating, and organising thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information

Psychiatric
Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hypersexuality (uncommon), psychosis (uncommon)

Metabolic
Weight loss, sleep disturbance

Others
Dysphasia (combination of motor and language difficulties), dysphagia (combination of motor problems, impulsivity, and distractibility)

Motor symptoms

The motor symptoms of Huntington's disease can be divided into two categories: added involuntary movements such as chorea, and impaired voluntary movements, which cause limb incoordination and impaired hand function. These symptoms are worsened by loss of postural reflexes. The pattern of symptoms tends to change over time, with chorea declining and dystonia, rigidity, and bradykinesia becoming more marked.

Cognitive symptoms

Cognitive impairment includes slowing of thought processing and deterioration of executive functions (high level cognitive processes that control other aspects of cognitive function). Typically, patients report difficulty with multitasking, concentration, and short term memory. Thinking style becomes more concrete and less efficient, and the planning, initiation, and organisation of time, thoughts, and activities become harder. People with Huntington's disease are often impulsive and develop psychomotor perseveration. Visuospatial perception can also deteriorate.[4 9]

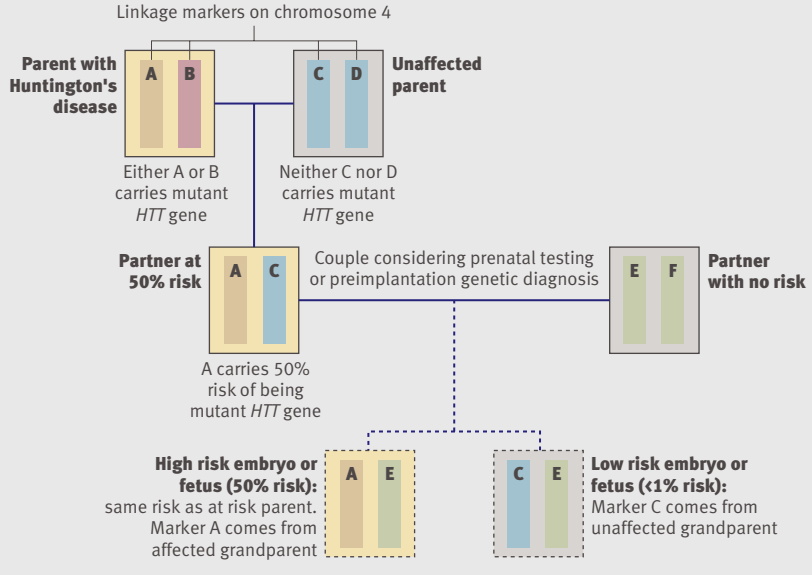

Fig 2 | Use of linkage analysis for prenatal testing. Adapted, with permission, from material of the Guy's and St Thomas' NHS Foundation Trust reproductive medicine clinic and assisted conception unit

Psychiatric symptoms

Depression is one of the most common psychiatric symptoms and occurs as part of the disease, rather than merely as a response to diagnosis. A recent survey of 2835 patients with the disease found that 40% had symptoms of depression, and 50% reported having sought treatment for depression in the past.[10] Other reported psychiatric symptoms include obsessive-compulsive symptoms and psychosis.[w3-w5]

It is important to recognise psychiatric symptoms in Huntington's disease so that symptomatic treatment can be offered. This may be difficult later in the disease because diagnoses may be obscured by other features of the disease; depression, for example, may be difficult to detect in a patient who has altered facial expressions and tone of voice. Conversely, metabolic symptoms such as weight loss and sleep disturbance may be wrongly attributed to depression.

Suicide risk

Patients with Huntington's disease are more likely than members of the general population to commit suicide according to a meta-analysis of studies that reported mortality associated with mental disorders (standardised mortality ratio of 290).[w6] A survey of 4171 carriers of the Huntington's gene with premanifest and manifest disease found that 17.5% had suicidal thoughts at or around the time of assessment and 10% of those surveyed had made at least one suicide attempt in the past.[11] Suicidal ideation was highest in gene carriers who were nearing the threshold of being diagnosed with manifest disease (those with soft motor signs of Huntington's disease), and in those who were beginning to lose their functional ability and independence (those with stage 2 disease). Risk factors for suicide in Huntington's disease include depression and impulsivity.[4] Some people with the disease also have suicidal thoughts in the absence of depression[w7]: for some, thoughts of suicide seem to be a rational response to their imminent loss of independence.

Metabolic symptoms

Huntington's disease causes metabolic symptoms, which include catabolic weight loss, endocrine dysfunction, and sleep disturbance.[12]

Advanced disease

By the time patients have endstage disease they are profoundly disabled. Communication may be severely limited and muteness is common, which can result in agitation and frustration. Huntington's disease does not cause global dementia, however, and the ability to recognise and interact with people is often preserved. Huntington's disease is a catabolic condition, and this, combined with marked dysphagia, means that it can be difficult to provide sufficient nutrition to maintain a patient's weight.

How is Huntington's disease inherited?

What is the genetic basis of the disease?

Huntington's disease is a single gene disease with autosomal dominant inheritance. The genetic abnormality is an expanded CAG trinucleotide repeat within the Huntingtin (*HTT*) gene on chromosome 4, and it can be identified through genetic testing.[13] The *HTT* gene encodes the protein huntingtin, which is essential for normal neural development,

Box 2 | Sources of information about symptoms of Huntington's disease

- The HDA website: contains easily accessible information about Huntington's disease (www.hda.org.uk/)
- The definitive book about Huntington's disease: *Huntington's disease*, 3rd ed. Bates GP, Harper PS, Jones L, eds. Oxford Monographs on Medical Genetics 45. Oxford University Press, 2002
- Further information about psychiatric symptoms: Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry* 2001;71:310-4
- Further information about psychiatric symptoms in premanifest disease: Julien CL, Thompson JC, Wild S, Yardumian P, Snowden JS, Turner G, et al. Psychiatric disorders in preclinical Huntington's disease. *J Neurol Neurosurg Psychiatry* 2007;78:939-43
- Further information about non-neurological features: Van der Burg JM, Bjorkqvist M, Brundin P. Beyond the brain: widespread pathology in Huntington's disease. *Lancet Neurol* 2009;8:765-74

although its functions are incompletely understood.[14 w8 w9] In Huntington's disease, the expanded *HTT* gene encodes a mutant form of huntingtin protein. The mutant protein causes or contributes to the development of Huntington's disease through many pathogenic mechanisms.[15]

Offspring of an affected parent have a 50% chance of inheriting the genetic abnormality, and males and females are affected equally. Huntington's disease does not skip generations.

What is the meaning of CAG repeat length in Huntington's disease?

A "normal" *HTT* gene has fewer than 36 repeats. The gene is abnormal, or expanded, if it has 36 or more repeats, and CAG repeats of 40 or more will always cause Huntington's disease. Genes with CAG repeat lengths between 36 and 39 show reduced penetrance, which means that some people with these lengths will develop Huntington's disease and some will not; those who do develop disease are likely to develop later onset disease.[w10] An intermediate repeat length between 29 and 35 does not cause the disease but may expand into the pathogenic range in future generations.

The instability of intermediate alleles is one cause of sporadic cases of Huntington's disease, in which the disease develops in someone with no apparent family history. Apparent sporadic Huntington's disease occurs in 6-8% of new cases of the disease,[w11 w12] and it can also be caused by unexpected or unknown paternity, or a parent dying before they develop symptoms of the disease.

CAG repeat length is related to age of onset of disease at a population level: the longer the CAG repeat length, the earlier the onset of symptoms tends to be. However, repeat length only accounts for 50-70% of this variance, and disease onset in an individual cannot be predicted reliably through genetic testing.[w15]

A PATIENT'S PERSPECTIVE

I am not as whole as I was. My thought processes have slowed down and it takes enormous self discipline to do ordinary things like getting dressed—it's exhausting. I recognised these changes in myself years before anyone else did, and it is important that other people (including healthcare professionals) just accept this—the changes don't have to be measurable. They can't reassure me that all is well but they can support me. By accepting that changes are happening, they give me permission to adapt my life at an early stage. I have changed my high powered job to an "ordinary" job, for example, which has taken pressure off me and allowed me to put energy into other things. The end stage of Huntington's disease will happen no matter what, but I will live most of my life before this point and I want to make the most of it.

Sue Walters, *Hertfordshire*

How is genetic testing undertaken?

Genetic testing for Huntington's disease is performed by measuring the CAG repeat length in the *HTT* gene. We will use the term "positive" test result to refer to CAG lengths in the pathogenic fully penetrant CAG repeat range of more than 39 repeats. Testing falls into two categories.

Diagnostic testing is carried out to confirm (or refute) the diagnosis in a patient with symptoms suggestive of Huntington's disease. It is a test for manifest disease and is most commonly undertaken by neurologists. A positive diagnosis has many implications for family members (especially children and siblings) and for the patient, and it is our experience that it is important to offer as much information as possible about the disease and the meaning of a positive diagnosis before testing. This is because family members' reactions and coping strategies are linked to how they find out that they are at risk themselves.

Predictive testing is carried out in a person who has no symptoms of the disease, but who is at risk because of their family history. It determines whether that person carries the expanded *HTT* gene and will develop Huntington's disease in the future. A positive predictive test result indicates that they will certainly develop Huntington's disease at some point in the future (unless they die of another cause in the meantime), but it does not tell them when this will happen or what the presenting symptoms will be. Reasons commonly cited for having predictive testing include wishing to relieve uncertainty, to inform decisions about reproduction, and to plan for the future.[16 17] Predictive testing is not performed in children because informed consent requires an adult understanding of the consequences. Consent for predictive testing by a parent would remove from a child their right to autonomy in choosing whether or not to be given this information.

Predictive testing for Huntington's disease is performed in specialist genetic centres and follows internationally agreed guidelines.[18-20] These include an initial session of pre-test counselling, followed by a period of reflection, and then a second session of counselling. Post-test counselling must also be available. On average, 5-20% of those at risk in the United Kingdom take up the option of predictive testing.[21 w18-w20]

What ethical considerations surround genetic testing?

Confidentiality and consent

According to internationally agreed guidelines,[18-20] strict confidentiality is observed before, during, and after predictive testing. No one other than the adult being tested is told about the process without their express permission. This includes partners and family members. Some people with positive predictive Huntington's disease test results choose not to inform their general practitioner. Written informed consent must be obtained from the patient before either predictive testing or diagnostic testing. If the patient lacks capacity to make the decision themselves for diagnostic testing, consent can be given by an authorised representative.

Having children

Deciding whether to have children is often difficult for people with or at risk of having an expanded *HTT* gene. A minority choose to have either prenatal testing or preimplantation genetic diagnosis, which ensures that their child has a less than 1% chance of carrying the expanded *HTT* gene.

Table 1 | Symptomatic management of movement disorder in Huntington's disease

Symptom	Drug class	Drug	Main adverse effects and treatment notes
Chorea	Atypical neuroleptics	Olanzapine	Sedation, parkinsonism, tardive dyskinesias and neuroleptic malignant syndrome but less risk than with older neuroleptics, raised triglycerides, weight gain from increased appetite which may be beneficial in Huntington's disease; caution should be exercised in patients with diabetes and blood glucose should be monitored; may rarely cause prolonged QT interval; useful if the patient also has agitation, irritability, and anxiety
	Atypical neuroleptics	Risperidone	As above but less effect on appetite
	Atypical neuroleptics	Quetiapine	As above but less effect on glucose
	Older neuroleptics	Sulpiride	Agitation, dystonia, akathisia, sedation, hypotension, dry mouth, constipation
		Haloperidol	Sedation, more parkinsonism, dystonia, akathisia, hypotension, constipation, dry mouth, weight gain, tardive dyskinesias, higher risk of neuroleptic malignant syndrome than with atypical neuroleptics
	Dopamine depleting agents	Tetrabenazine	Depression and sedation
Myoclonus, chorea, dystonia, rigidity, spasticity	Benzodiazepines	Clonazepam	Sedation, ataxia, apathy, cognitive impairment may be exacerbated, withdrawal seizures
Myoclonus	Anticonvulsant	Sodium valproate	Gastrointestinal disturbance, liver dysfunction, weight gain, blood dyscrasias, hyperammonaemia
		Levetiracetam	Gastrointestinal disturbance, rash, mood changes, myalgia
Rigidity (particularly associated with juvenile Huntington's disease or young adult onset parkinsonian phenotype)	Amino acid precursor of dopamine	Levodopa	Gastrointestinal disturbance, postural hypotension, insomnia, agitation, psychiatric symptoms
Rigidity, spasticity	Skeletal muscle relaxants	Baclofen, tizanidine	Sedation, drowsiness, confusion, gastrointestinal disturbance, hypotension
Bruxism, dystonia	Inhibits acetylcholine release at neuromuscular junction to cause muscle paralysis	Botulinum toxin	May paralyse nearby muscles

Prenatal testing

Prenatal testing is usually carried out via chorionic villus sampling between 11 and 13 weeks of pregnancy. Pre-test counselling is important: potential parents need to be sure that they will terminate the pregnancy if their fetus is found to have an expanded *HTT* gene, otherwise their child will grow up in the shadow of a predictive test for which they did not consent.

Preimplantation genetic diagnosis

In this technique, embryos are created using normal in vitro fertilisation procedures and then tested for the expanded *HTT* gene. Unaffected embryos are implanted. Overall, about one in five cycles results in a live birth, but success rates vary. The Human Fertilisation and Embryology Authority website contains more details (www.hfea.gov.uk/).

Exclusion (non-disclosing) prenatal testing and preimplantation genetic diagnosis

These use linkage techniques, rather than testing for the CAG expansion (see fig 2 for more details), and potential parents do not find out their own gene status. A "high risk" result means that the fetus is at 50% risk of developing Huntington's disease—the same as the at risk parent. The couple therefore chooses to terminate a pregnancy at 50% risk.

What are the implications of a positive gene test for the individual?

Emotional implications

A patient who receives a diagnosis of manifest Huntington's disease learns that he or she has a slowly progressive incurable disease. A person who receives a positive predictive test experiences the extra burden of being uncertain when the disease will begin to take effect. Most people who have genetic testing for Huntington's disease will have watched a parent develop the disease, will be familiar with the change in personality and cognition that it causes, and will know what effect their illness will have on those around them.

In 1996, one study followed up 135 Canadians who had entered a predictive testing programme.[w21] Adverse events, including psychological distress, substance misuse, and relationship breakdowns, were recorded in seven of the 37 who received a positive result compared with eight of the 58 who received a negative result. (The remaining subjects received equivocal results or chose not to proceed with testing.) One subject in each group reported suicidal ideation.

A positive predictive test can come as a relief because some people find a positive test result easier to cope with than the uncertainty of being at risk. The minority who choose it are a self selecting group, and the aim of genetic counselling is to ensure that they are equipped to deal with their predictive test result.

Practical implications: insurance and employment

In 2001, the Association of British Insurers (ABI; the trade association for the UK insurance industry; www.abi.org.uk/) and the UK government agreed a moratorium on access to any predictive genetic test results by insurance companies who are ABI members (this is due for review in 2011). In general, insurers will weight applicants who have a family history of Huntington's disease but cannot require them to take a predictive genetic test. People at risk of Huntington's disease can apply for a certain amount of life insurance, critical illness insurance, and income protection without disclosing the results of any predictive genetic test. Huntington's disease is, however, the one disease that is exempt from a total ban on disclosure; applicants must disclose Huntington's disease predictive test results if they apply for life insurance over £500 000. A negative predictive test result will bring insurance premiums back in line with those of people without a family history of Huntington's disease. A positive predictive test does not need to be declared when applying for travel insurance in the UK, but manifest disease does.

Under the 1995 Disability Discrimination Act in the UK, it is illegal for employers to discriminate against someone who is disabled by dismissing them or by treating them

Table 2 | Symptomatic management of psychiatric symptoms in Huntington's disease

Symptom	Drug class	Drug	Main adverse effects and treatment notes
Psychosis	Atypical neuroleptics	Olanzapine, risperidone, quetiapine	See table 1. Use carefully in elderly people because of the increased risk of stroke with olanzapine and risperidone in this population
Treatment resistant psychosis	Neuroleptics	Clozapine	As for the other neuroleptics, plus agranulocytosis, myocarditis, and cardiomyopathy. Requires blood monitoring
Psychosis with prominent negative symptoms	Neuroleptics	Aripiprazole	Parkinsonism, akathisia, drowsiness, gastrointestinal disturbance, tremor, blurred vision
Depression, anxiety, obsessive-compulsive symptoms, irritability, aggression	Selective serotonin reuptake inhibitors (SSRI)	Citalopram	Gastrointestinal disturbance, hypersensitivity reactions, drowsiness, syndrome of inappropriate antidiuretic hormone secretion (SIADH), postural hypotension
		Fluoxetine	As for citalopram, but also sleep disturbances
		Paroxetine	As for other SSRIs, but also raised cholesterol
		Sertraline	As for other SSRIs
	Presynaptic α_2 adrenoceptor antagonist (increases central noradrenaline and serotonin activity)	Mirtazapine	Weight gain, oedema, sedation, headache, dizziness, tremor; useful when insomnia is a problem because it has sedative properties
	Serotonin and noradrenaline reuptake inhibitor	Venlafaxine	Hypertension, gastrointestinal disturbance, hypersensitivity reactions, drowsiness, agitation, SIADH, palpitations
Irritability, aggression	Neuroleptics	Olanzapine, risperidone, quetiapine	See above
Altered sleep-wake cycle	Hypnotics	Zopiclone, zolpidem	Drowsiness, confusion, memory disturbance, gastrointestinal disturbance
Mood stabilisers	Anticonvulsants	Sodium valproate	See above
		Lamotrigine	Hypersensitivity reactions, blood dyscrasias, dizziness, gastrointestinal disturbance, depression
		Carbamazepine	Hypersensitivity reactions, drowsiness, blood dyscrasias, hepatitis, hyponatraemia, dizziness, gastrointestinal disturbance

negatively because of their disability. We strongly recommend that patients with Huntington's disease who feel that their ability to work is deteriorating inform their employers about their diagnosis to ensure that their job is legally protected. Once diagnosis is revealed, regular assessment should take place according to occupational risk. The legal situation for people at risk of Huntington's disease because of their family history is less clear cut, and there is currently no law in the UK to prevent discrimination against those with a genetic diagnosis (in employment, or elsewhere). Research on genetic discrimination in Huntington's disease is limited, but a recent survey of 233 tested and untested people at risk of Huntington's disease in Canada found that 6.4% reported genetic discrimination related to employment.[w22] Anecdotal evidence also suggests that some premanifest gene carriers have been discriminated against in the UK.

What are the implications of a positive Huntington's disease gene test for the family?

A positive predictive or diagnostic Huntington's disease test has a huge effect on the partner and family of the person tested. Someone close to the person tested faces the prospect of becoming a carer, often when relatively young, and probably for many years. A new diagnosis of Huntington's disease has implications for siblings and children who suddenly become at risk of acquiring the disease.

The dynamics of families affected by Huntington's disease are often complicated, particularly between those who do and those who do not carry the expanded gene. It may create supportive and close knit families, but it can also be divisive. The result is often a high level of resilience and care within the family, mixed with anger, resentment, and guilt. Guilt may be felt by a parent who has passed on their disease gene to a child, or who has become symptomatic and now sees himself or herself as a burden to the family. Receiving a negative test result when other family members have tested positive can be an isolating experience and may lead to survivor guilt.

Most affected families will contain more than one person with the disease, with several more at risk of developing the disease in the future, creating a scenario where one person first endures the burden of being a carer and being bereaved by the disease, and later being a patient who needs care.

How is Huntington's disease managed?

The aim of treatment is to manage symptoms and improve quality of life. No current treatments can slow disease progression, although promising disease modifying treatments are being tested in animal models.[15 22] There are many effective options for symptomatic management, however, both drug based and non-drug based.[23 24] Tables 1 and 2 summarise those drugs commonly used for symptom management. Their choice is based mainly on clinical experience because the evidence base for drugs in Huntington's disease is small.[25-28] Tetrabenazine has the best evidence of efficacy in Huntington's disease and has been shown to reduce chorea in a randomised controlled clinical trial.[w23] Box 2 contains details of where to access further information about drug treatments in Huntington's disease.

Many non-drug based measures are effective in the management of Huntington's disease, and these are often more helpful than drugs (table 3).[3 29] Because evidence is limited, their use is based on extensive clinical experience.

We recommend that patients are referred to a specialist multidisciplinary Huntington's disease clinic where possible, so that they can access care from healthcare professionals experienced in the management of the disease. Support from professionals in the community remains vital, and optimal care is typically provided by a multidisciplinary team that includes some or all of the following: general practitioners, neurologists, geneticists, psychiatrists, physiotherapists, occupational therapists, speech and language therapists, dietitians, community mental health teams, and social workers. HDA advisers are available throughout England and Wales to support patients and their families, and to provide educational input for healthcare professionals caring for people with the disease (www.hda.org). The Scottish

Table 3 | Non-drug based management of Huntington's disease

Feature of disease	Examples of management measures
Gait disturbance and chorea	Physiotherapy to optimise and strengthen gait and balance, and to assess for walking aids; occupational therapy assessment to modify home environment and improve safety; weighted wrist bands to combat limb chorea
Cognitive symptoms	Ensure every day has a structure to overcome apathy and difficulty in initiating activities (occupational therapy can advise on this); maintain routines to reduce need for flexibility
Social problems	Carers to help at home, residential or nursing home care, day centres to maintain social interactions
Communication	Speech and language therapy to optimise speech and later in disease to assess for communication aids; ensure patient has time to comprehend and respond to speech, and that information is presented simply
Nutrition	Speech and language therapy to advise on safest food consistencies at different stages of disease, and, in later disease, to advise on need to consider enteral nutrition; dietitian to optimise nutritional intake, especially adequate energy intake; minimise distractions to optimise swallowing safety
Psychological problems	Develop strategies to deal with cognitive and emotional challenges of disease using counselling or cognitive behavioural therapy

Huntington's Association and the Huntington's Disease Association of Northern Ireland provide similar support.

Managing the movement disorder

The first step is to decide whether symptoms need treating. Patients are often not bothered by early chorea, for example, and may not even be aware of it. As chorea develops, it can interfere with voluntary activities like writing or eating and may cause falls, making intervention necessary. Chorea can be distressing in itself, and patients often find themselves accused of drunkenness by people unaware of their diagnosis.

Non-drug interventions should be considered first. Devices such as padded chairs or wrist and ankle weights to reduce the amplitude of chorea may be helpful. Shoes with non-slip soles and grab rails around the home can improve safety, and assessment of the home by an occupational therapist may be useful. Physiotherapy can also help optimise mobility and preserve independence for as long as possible. Like most involuntary movements, chorea is worsened by stress, anxiety, and depression, so treating these and providing a calm predictable environment are beneficial.

Drugs are unlikely to prevent chorea completely but may reduce symptoms considerably. Tetrabenazine is generally the first choice. It can exacerbate or trigger psychiatric symptoms, so it should be avoided in patients with a history of depression or other psychiatric disorders, and in these patients, or in those in whom symptoms are not controlled with tetrabenazine, the atypical neuroleptics are helpful.

Movement suppressing drugs used in the earlier stages may however exacerbate the impaired movements that develop later on. They will often need to be reduced and eventually stopped, so regular reassessment is vital.

Box 3 | Sources of information about the management of Huntington's disease

- As well as containing general information about Huntington's disease, the HDA website contains information about disease management, including extensive advice on non-medical management (www.hda.org.uk/). Guidelines for allied health professionals caring for patients with Huntington's disease (for example, physiotherapy, speech and language therapy, dietary advice) are accessible via the site
- An excellent review of management: Phillips W, Shannon KM, Barker RA. The current clinical management of Huntington's disease. *Mov Disord* 2008;23:1491-504
- Cochrane review of medical treatment: Mestre T, Ferreira J, Coelho MM, Rosa M, Sampaio C. Therapeutic interventions for symptomatic treatment in Huntington's disease. *Cochrane Database Syst Rev* 2009;3:CD006456
- A comprehensive review of an ideal care pathway for Huntington's disease: shown in figure 2 in the article Huntington's disease: GP guide to clinical management. El-Nimr G, Barrett K. *Prescriber* 19 May 2006
- A good source of information about palliative care in Huntington's disease (some comments are specific to the US, but the general principles are universal): Moskowitz CB, Marder K. Palliative care for people with late-stage Huntington's disease. *Neurol Clin* 2001;19:849-65

Managing cognitive and psychiatric manifestations

It is important to ask depressed patients about suicidal thoughts, and to take a proactive approach to the treatment of psychiatric symptoms. Treatment of depression in Huntington's disease is with standard antidepressants. Although there is not an established evidence base for the treatment of depression in Huntington's disease, our experience is that antidepressants are often effective. Psychological treatments, such as cognitive behavioural therapy, can also be helpful in selected patients and may be a useful way for people with premanifest disease to learn cognitive strategies that will stand them in good stead once they develop cognitive and psychiatric symptoms. One case study has reported benefit for a patient with premanifest disease.[w24] Support from local community mental health teams is often invaluable.

No drug treatments are available for cognitive symptoms, but coping strategies can often be adopted to overcome problems or compensate for them. Moving into a quieter office and reducing workload can be helpful when it becomes difficult to concentrate in a busy office, for example. Employers have a statutory duty to optimise the working environment for people with a disability where possible.

Apathy is a challenging symptom to manage and can be difficult to differentiate from depression. Patients often find that having an appointment to aim for, such as coffee with a friend, helps them to initiate activities and organise their behaviour. It can be difficult for people with Huntington's disease to initiate activities, but once started they are often able to participate fully with encouragement and support from carers.

End of life care

Planning for end of life care raises several ethical problems that often relate to how far medical interventions should be taken in patients who no longer have the capacity to make their wishes known. We find that advanced decisions to refuse treatment (previously known as advanced directives) can be extremely helpful. They give patients the security of knowing that their wishes will be carried out, even if they are no longer able to make decisions or communicate, and they relieve relatives of the responsibility of making choices. Advanced decisions to refuse treatment and end of life care should be raised as early as possible so that they can be discussed by the patient and their loved ones. The Independent Mental Capacity Advocate service (www.dh.gov.uk/en/SocialCare/Deliveringadultsocialcare/MentalCapacity/IMCA/index.htm) provided via the Department of Health can be helpful if a patient does not have capacity and his or her next of kin is unable or unwilling to make decisions on the patient's behalf.

As Huntington's disease progresses, it often becomes increasingly difficult to provide care at home, and a nursing home may be the best option. Insertion of a gastrostomy tube

CURRENT RESEARCH

- There is currently a major push to find disease modifying drugs and new treatments for the symptoms of Huntington's disease, and many new developments have been made in recent years
- In February 2010, the results of the MermaiHD study were announced as a press release: pridopidine, a dopamine stabiliser (also known as Huntexil, previously known as ACR16), was shown to improve voluntary motor symptoms in a phase III trial of 437 patients with Huntington's disease. Publication in a peer reviewed form is awaited
- Previous clinical trials have evaluated creatine and coenzyme Q10 among other compounds, but have not demonstrated efficacy. Many patients continue to buy them over the counter and comparison trials of the two substances, funded by the National Institutes for Health, are ongoing
- A phrase III trial of latrepirdine (Dimebon) is currently taking place in multiple sites, including several in the UK
- Exciting progress has been made recently in identifying several other pathways that are potential targets for future therapeutic intervention and clinic trials. This is too large a subject to cover in detail, but see Imarisio et al for a comprehensive review.[15] Potential therapeutic approaches include:
  - Enhancing clearance of mutant huntingtin by cellular clearance mechanisms: several compounds being tested in mouse models of Huntington's disease aim to promote clearance of the mutant protein, huntingtin, which is generated by the expanded *HTT* gene
  - Histone deacetylase inhibitors: these target the transcriptional dysregulation that occurs early in the pathogenesis of Huntington's disease
  - Inhibitors of proteolytic cleavage of full length mutant huntingtin: these would prevent production of the potentially toxic N-terminal fragment
  - Gene silencing: to switch off expression of the mutant gene itself
- To achieve optimal effect, future disease modifying treatments will probably consist of a combination of treatments targeting key pathogenic pathways, similar to the treatment of HIV or cancer
- Much progress has been made in developing and evaluating sensitive biomarkers that will help to measure the effects of disease modifying treatments in future clinical trials, particularly in the premanifest and early stages of the disease. Track-HD[7] and Predict-HD[9] are major international collaborative studies that have increased our understanding of the course of Huntington's disease and which biomarkers are the best for monitoring this

ADDITIONAL EDUCATIONAL RESOURCES

These websites are accessible and excellent sources of information for both patients and families and healthcare professionals:

- www.hda.org.uk/
- www.hdlighthouse.org/
- http://hopes.stanford.edu/

may be appropriate in patients who are unable to maintain adequate nutrition and body weight. Box 3 contains sources of information for palliative management in Huntington's disease.

Conclusions

Managing the many facets of Huntington's disease can be challenging and is best served within multidisciplinary settings. We continue to learn about how to improve our services from our patients and their families. In the future treatments might be initiated in the premanifest phase, with the hope of delaying or halting the disease process itself.

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