HUNTINGTON’S DISEASE: CLINICAL PRESENTATION AND TREATMENT

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Huntington’s disease (HD) is a devastating inherited neurodegenerative disease characterized primarily by progressive motor, cognitive, and psychiatric symptoms. It is caused by autosomal dominant inheritance of an expanded CAG repeat within the Huntington’s gene on chromosome 4. In this chapter, we characterize the typical and variant motor phenotypes of the disease and then proceed to describe the cognitive and psychiatric profile. We then give an overview of a suggested multidisciplinary approach to the management of HD, emphasizing the fact that it is a disease which impacts on entire families rather than affecting individuals in isolation. We then describe the pharmacological and nonpharmacological options available for management of specific symptoms.
I. Clinical Presentation and Genetics

A. INTRODUCTION

Huntington’s disease (HD) is a devastating inherited neurodegenerative disease characterized primarily by progressive motor, cognitive, and psychiatric symptoms. The mean age of onset of symptoms is 40 years, but juvenile (onset < 20 years) and older onset (> 70 years) forms also exist. 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: there are also many nonmotor symptoms which may in fact be more disabling and distressing than the motor symptoms. These are discussed in more detail below (Craufurd and Snowden, in press; Nance and Westphal, in press; Rothlind et al., 1993). The pattern of symptoms can vary markedly between one patient and the next, even within the same family, so it is crucial to tailor management to every individual. In this chapter, we present a framework within which to address these issues.

B. EPIDEMIOLOGY

HD occurs in all racial groups but is most common in people of Northern European origin. Its prevalence in the Western hemisphere is approximately 7-10/100,000 (Harper, 1992).

C. THE GENETICS OF HUNTINGTON’S DISEASE

HD is a single-gene disease; it is caused by autosomal dominant inheritance of an expanded CAG trinucleotide repeat within the Huntington (HTT) gene on chromosome 4. This can be identified through genetic testing (The Huntington’s Disease Collaborative Research Group, 1993). The HTT gene codes for the protein huntingtin, which is essential for normal neural development, though its functions are incompletely understood (Cattaneo et al., 2005; Walker, 2007; Young, 2003). In HD, the expanded HTT gene codes for a mutant form of huntingtin protein which causes or contributes to the development of symptoms though various pathogenic mechanisms (Imarisio et al., 2008).

A “normal” Huntington 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 HD. Genes with CAG repeat lengths of between 36 and 39 show reduced penetrance, which means that some people with these lengths will develop HD and some will not. Those who do develop disease are likely to develop later onset disease
An intermediate repeat length between 29 and 35 does not cause HD, but may expand into the pathogenic range in future generations.

The instability of intermediate alleles is one cause of apparently sporadic cases of HD, in which the disease develops in someone with no apparent family history of the disease. Apparently sporadic HD occurs in 6–8% of new cases of HD (Almqvist et al., 2001; Siesling et al., 2000), and can also be due to unexpected or unknown paternity, or a parent dying before they develop symptoms of the disease. Instability of the CAG repeat expansion can also cause “genetic anticipation,” in which the CAG repeat length increases and causes the onset of the disease at a younger age in the affected offspring of someone with HD than in the parents themselves. Genetic anticipation is more common when the expanded allele is inherited from a father than from a mother. 90% of people with juvenile HD (with CAG repeats typically >60) inherit the mutation from their father (Harper and Jones, in press; Barbeau, 1970).

The following sections describe clinically relevant aspects of the genetics of HD. For more information, please see the authors’ recent review of HD (Novak and Tabrizi, 2010).

1. Genetic testing for Huntington’s disease

Genetic testing for HD is performed through quantification of the CAG repeat length in the HTT gene. We use the term “positive” genetic test result to refer to CAG lengths in the pathogenic fully penetrant expanded CAG repeat range of >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 HD, whereas predictive testing is carried out in a person who has no symptoms of HD, but who is at risk because of their family history. Predictive testing determines whether an individual carries the expanded HTT gene and will develop HD in the future. A positive predictive test result indicates that they will certainly develop HD at some point in the future (unless they die of another cause in the meantime), but does not tell them when this will happen or what the presenting symptoms will be. Predictive testing for HD is only performed in specialist genetic centers and follows internationally agreed guidelines (Craufurd and Harris, 1989; International Huntington Association, 1994; Went, 1990). These include an initial session of pretest counseling, followed by a period of reflection and then a second session of counseling. Posttest counseling must also be available and strict confidentiality must be observed. Both emotional and practical issues are discussed. Insurance and mortgage eligibility, for example, may be affected by a positive predictive test result.

2. Reproductive options

Deciding whether or not 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 ensure that their child has a <1% chance of carrying the expanded \textit{HTT} gene.

\textit{Prenatal testing}

Prenatal testing is usually carried out via chorionic villus sampling between 11 and 13 weeks of pregnancy. Pretest counseling is important: potential parents need to be sure that they will terminate the pregnancy if their fetus is found to have an expanded \textit{HTT} gene, otherwise their child will grow up in the shadow of a predictive test for which they did not consent. This would violate the autonomy of the child.

\textit{Preimplantation genetic diagnosis (PGD)}

Preimplantation genetic diagnosis (PGD) is available through specialist units. In PGD, embryos are created using normal IVF procedures and then tested for the expanded \textit{HTT} gene. Unaffected embryos are implanted. Overall, about one in five cycles results in a live birth, but success rates vary.

\textit{Exclusion (nondisclosing) prenatal testing and PGD}

Exclusion (nondisclosing) prenatal testing or PGD can be carried out for couples in which one partner is at risk but does not wish to have a predictive test themself: the potential parents do not find out their own HD gene status. Linkage techniques are used. A “high risk” result means that the fetus is at 50% risk of developing HD—the same as its at-risk parent. The couple undergoing this test therefore chooses to terminate a pregnancy at 50% risk. Clearly this test requires detailed discussion with the couple beforehand.

D. THE COURSE OF THE DISEASE AND ITS RELATIONSHIP WITH CAG REPEAT LENGTH

An individual with an expanded HTT gene will usually develop symptomatic, or “manifest,” HD in their 30s or 40s. This will generally progress to end-stage disease over 15–30 years. The onset of manifest HD is currently defined as the point at which characteristic motor signs develop (Huntington Study Group, 1996); prior to this point, the individual is classed as a “premanifest gene carrier.” The distinction between premanifest and manifest disease is somewhat arbitrary, however, as most patients develop some or all of cognitive, psychiatric or subtle motor symptoms during the premanifest (“prodromal”) period, and this often occurs many years before any “hard” motor signs are seen (Paulsen et al., 2006, 2008; Tabrizi et al., 2009). Patients may present initially with any symptom. Chorea and loss of balance are early symptoms that patients themselves often
notice, though frequently families notice cognitive or personality changes prior to this.

The typical pattern of disease progression is shown in Fig. 1 (Ross and Tabrizi, 2011).

The expanded 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 (Andrew et al., 1993; Brinkman et al., 1997; Duyao et al., 1993; Snell et al., 1993; Stine et al., 1993; Langbehn et al., 2004). However, repeat
length only accounts for between 50 and 70% of this variance, so disease onset in an individual cannot be predicted reliably through genetic testing (Wexler et al., 2004). This can be seen in Fig. 2 (Andrew et al., 1993). Use of the CAG repeat length to predict disease onset is useful in Huntington’s disease research, but has minimal relevance to the management of individual patients. The CAG repeat length is also associated with the rate of disease progression, but less strongly than with the age of symptom onset (Rosenblatt et al., 2006; Ravina et al., 2008).

E. STAGING OF HUNTINGTON’S DISEASE

In clinical practice, staging in HD is usually based on the HD-specific Total Functional Capacity (TFC) scale (Shoulson and Fahn, 1979). Staging is based on functional ability in recognition of the fact that some symptoms of HD are more functionally disabling than others (Rothlind et al., 1993). A score is given according to an individual’s ability to function independently in each of four domains—occupation, finances, domestic chores and activities of daily living—and the level of nursing care they need. The scale covers all stages of the disease, ranging from minimal functional impairment to requiring complete support in every domain.
The Unified Huntington’s Disease Rating Scale (UHDRS) (Huntington Study Group, 1996) is a clinical rating scale used primarily for research purposes. It is used to assess patient ability in four domains: functional capacity (assessed using the Shoulson–Fahn TFC scale), motor function, cognition, and behavior.

F. HUNTINGTON’S DISEASE IS A DISEASE OF THE FAMILY

HD has a profound impact on those around an affected individual as well as on that individual him or herself. The inexorable progression of the disease is painful for families and friends to watch, and most affected families will include more than one affected individual, with several more at risk of developing the disease in the future. In addition, the burden of being first a carer and later a patient is handed down through the generations; for many people, being tested positive for the HD gene carries the dual consequences of being diagnosed with a disease that has taken the life of a parent, and passing on the burden of being a carer and perpetuating the cycle to one’s own children. HD is often little understood by those who have not experienced it first hand, so having supportive family members who are familiar with the disease can be particularly important.

G. OVERALL PRINCIPLES OF MANAGEMENT OF HUNTINGTON’S DISEASE

As mentioned earlier, HD can cause markedly different patterns of symptoms from one patient to the next, even within the same family. It is therefore crucial to tailor management to each individual, and to ensure that the priorities of the patient are listened to when formulating management plans. Patients may be less concerned by their chorea than their family is, for example (and, in fact, it is very common for people with mild chorea not to be aware of it at all). If this is the case, it is important not to medicalize the person with HD or to expose them to potential drug side-effects by attempting to treat a symptom which is not actually causing a problem: the aim of current treatments for HD is to manage symptoms and improve quality of life (Novak and Tabrizi, 2010). One caveat to this, however, is that it is common for patients to lack insight into their symptoms; carer input is therefore invaluable when assessing someone with HD and deciding which symptoms are causing difficulties. The social and financial impact of HD can also be considerable and this should always be considered when assessing anyone with HD.

There are no treatments available to slow disease progression yet, but there are many effective options for symptomatic management, including both
pharmacological and nonpharmacological measures (Mestre et al., 2009; Phillips et al., 2008). The evidence base for drugs in HD is very small (Adam and Jankovic, 2008; Bonelli and Hofmann, 2007; Mason and Barker, 2009; Priller et al., 2008) so the choice of pharmacological agents is based mainly on clinical experience. Nonpharmacological measures are often more helpful than pharmacological measures (Nance, 2007; Nance and Westphal, in press); once again, limited evidence is available, but recommendations are based on extensive clinical experience. Further details are given in subsequent sections of this chapter.

The provision of care in HD usually requires a multidisciplinary approach (Nance, 2007; Nance and Westphal, in press). Patients usually benefit from referral to a specialist multidisciplinary HD clinic where possible, from which they can access care from a range of healthcare professionals experienced in the management of HD. Support from professionals in the community remains vital, and optimal care is typically provided from a multidisciplinary team which includes some or all of the following: general practitioners, neurologists, geneticists, psychiatrists, physiotherapists, occupational therapists, speech and language therapists, dieticians, community mental health teams, and social workers (Novak and Tabrizi, 2010). Table I gives an overview of the multidisciplinary nonpharmacological management of HD. Early involvement is recommended so that patients learn how to manage their symptoms while they still have the cognitive capacity to adapt and learn new skills.

Table I

<table>
<thead>
<tr>
<th>Feature of Disease</th>
<th>Examples of Management Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait disturbance and chorea</td>
<td>Physiotherapy to optimize and strengthen gait and balance, and to assess for walking aids; occupational therapy assessment to modify home environment to improve safety; weighted wrist bands to combat limb chorea</td>
</tr>
<tr>
<td>Cognitive symptoms</td>
<td>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</td>
</tr>
<tr>
<td>Social support</td>
<td>Carers to help at home; residential or nursing home care; day centers to maintain social interactions</td>
</tr>
<tr>
<td>Communication</td>
<td>Speech and language therapy to optimize 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</td>
</tr>
<tr>
<td>Nutrition</td>
<td>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; dietician to optimize nutritional intake, especially adequate caloric intake; minimize distractions to optimize swallowing safety</td>
</tr>
<tr>
<td>Psychological therapy</td>
<td>Develop strategies to deal with cognitive and/or emotional challenges of disease using counseling or CBT</td>
</tr>
</tbody>
</table>
Advisors and local groups linked with HD support organizations can play an invaluable role in supporting patients and their families. These organizations include the HD Association (HDA) in England and Wales and the HD Society of America (HDSA); many other countries have similar organizations (the International Huntington Association website, www.huntington-assoc.com, includes contact details for these). Care advisors can also provide educational input for healthcare professionals caring for people with HD. In some countries, specific groups exist to support young people affected by HD and can be accessed via the main support organizations.

II. The Clinical Phenotype and its Management

A. The Motor Disorder

The motor symptoms of HD 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 in typical adult-onset HD: typically chorea dominates in early disease, but then tends to decline as the disease progresses, with dystonia, rigidity, and bradykinesia then becoming more marked (Novak and Tabrizi, 2010). In general, these later symptoms tend to be more functionally incapacitating than the more readily recognized chorea. The change in symptomatology over time is particularly important when considering pharmacotherapy. Movement-suppressing medications used in the earlier stages of the disease may exacerbate the impaired movements that develop later on. They will often need to be reduced, and eventually stopped, so regular reassessment is vital.

A summary of the pharmacological treatments of the movement disorder is given in Table II.

1. Chorea

The first step in managing the movement disorder is to decide whether symptoms need treating. This is particularly relevant for chorea; patients are often not bothered by early chorea, and may not even be aware of it (Novak and Tabrizi, 2010). As chorea develops, however, it tends to become more problematic and to interfere with voluntary activities like writing or eating, and frequently causes falls. Chorea can also be distressing in itself, and patients often find themselves accused of drunkenness by people unaware of their diagnosis. These issues may be indications for treatment.
### Table II
Symptomatic Management of the Huntington’s Disease Motor Disorder (Reproduced from "Huntington’s Disease" by MJU Novak and SJ Tabrizi by Kind Permission of the Publisher).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug Class</th>
<th>Medication</th>
<th>Main Adverse Effects and Treatment Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea</td>
<td>Atypical neuroleptics</td>
<td>Olanzapine</td>
<td>Sedation, parkinsonism, tardive dyskinesias but less risk than with older neuroleptics raised triglycerides, weight gain from increased appetite which may be beneficial in HD. Caution should be exercised in patients with diabetes and blood glucose monitored. May rarely cause prolonged QT interval. Useful if also significant agitation, irritability and anxiety</td>
</tr>
<tr>
<td></td>
<td>Atypical neuroleptics</td>
<td>Risperidone</td>
<td>As above but less effect on increasing appetite.</td>
</tr>
<tr>
<td></td>
<td>Atypical neuroleptics</td>
<td>Quetiapine</td>
<td>As above, less effects on lipids and glucose.</td>
</tr>
<tr>
<td></td>
<td>Older neuroleptics</td>
<td>Sulpiride</td>
<td>Agitation, dystonia, akathisia, sedation, hypotension, dry mouth, constipation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>Sedation, more parkinsonism, dystonia, akathisia, hypotension, constipation, dry mouth, weight gain, higher risk of neuroleptic malignant syndrome than atypical neuroleptics</td>
</tr>
<tr>
<td></td>
<td>Dopamine depleting agents</td>
<td>Tetrabenazine</td>
<td>Depression and sedation.</td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
<td>Clonazepam</td>
<td>Sedation, ataxia, apathy, cognitive impairment may be exacerbated, withdrawal seizures.</td>
</tr>
<tr>
<td>Chorea</td>
<td></td>
<td>Sodium valproate</td>
<td>GI disturbance, weight gain, blood dyscrasia, hyperammonemia</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td>Levetiracetam</td>
<td>GI disturbance, rash, mood changes, myalgia</td>
</tr>
<tr>
<td>R rigidity</td>
<td></td>
<td>Levodopa</td>
<td>GI disturbance, postural hypotension, insomnia, agitation, psychiatric symptoms</td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
<td>Anticonvulsant</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
<td>Sodium valproate</td>
<td>GI disturbance, weight gain, blood dyscrasia, hyperammonemia</td>
</tr>
<tr>
<td>R rigidity (particularly associated with juvenile HD or young adult-onset Parkinsonian phenotype)</td>
<td>Amino acid precursor of dopamine</td>
<td>Levetiracetam</td>
<td>GI disturbance, rash, mood changes, myalgia</td>
</tr>
<tr>
<td>R rigidity</td>
<td></td>
<td>Levodopa</td>
<td>GI disturbance, postural hypotension, insomnia, agitation, psychiatric symptoms</td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
<td>Anticonvulsant</td>
<td></td>
</tr>
<tr>
<td>Bruxism</td>
<td></td>
<td>Botulinum toxin</td>
<td>May paralyze nearby muscles</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td>Botulinum toxin</td>
<td></td>
</tr>
<tr>
<td>Acetylcholine release</td>
<td></td>
<td>Botulinum toxin</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular junction to cause muscle paralysis</td>
<td></td>
<td>Botulinum toxin</td>
<td></td>
</tr>
</tbody>
</table>
Nonpharmacological interventions should be considered first. Chorea often varies with posture or positioning, and assistive devices, such as padded chairs or wrist and ankle weights to reduce chorea amplitude, may be helpful. Wearing shoes with nonslip soles and installing grab rails around the home can improve safety, and occupational therapy assessment to assess the home environment is often extremely useful. Physiotherapy is also helpful to optimize mobility and can be beneficial at an early point in the disease to preserve mobility and independence for as long as possible (Novak and Tabrizi, 2010).

Stress, anxiety, and depression can all worsen chorea, so measures to treat these are often helpful. Creating a calm and predictable environment is also beneficial.

If these measures are not sufficient to control symptoms, medications can be tried. These are unlikely to obliterate chorea, but can dampen down symptoms considerably. There are three different classes of medication that are commonly used: neuroleptics (e.g., olanzapine, risperidone), benzodiazepines (e.g., clonazepam, diazepam), and dopamine depleting agents (e.g., tetrabenazine). As mentioned above, there have been very few systematic clinical trials comparing the efficacy of these drugs and so management is primarily based on the opinion of experts rather than on a substantial evidence base. Choice is often dependent on consideration of the side-effect profile of each drug class.

Tetrabenazine has the best evidence of efficacy in HD and has been shown to reduce chorea in a randomized controlled clinical trial (Huntington Study Group, 2006). It is frequently the first choice of medication for uncomplicated chorea as although it shares some of the side effects of the neuroleptics, they tend to be milder. In addition, tetrabenazine has not been shown to cause tardive dyskinesia. (Tardive dyskinesia is of particular concern in HD because it can be difficult to detect in someone with a movement disorder.) Tetrabenazine can, however, exacerbate or trigger psychiatric symptoms so should be avoided in patients with a history of depression or other psychiatric disorders; in these patients, or in those in whom symptoms are not controlled with tetrabenazine, neuroleptics are helpful.

CYP2D6 (cytochrome P450 2D6) is integral in the metabolism of tetrabenazine. To avoid reduced clearance, tetrabenazine should therefore be used with care in patients who are also taking drugs with a CYP2D6 inhibitory effect. CYP2D6 inhibitors include fluoxetine, paroxetine and fluvoxamine; noninhibitory alternatives include citalopram, escitalopram and sertraline (Guay, 2010).

Neuroleptics are used to treat chorea by harnessing the movement suppression that is seen as an undesirable side-effect when the same drugs are used to treat psychosis. In the past, “typical” neuroleptics like haloperidol were frequently used, but the “atypical” neuroleptics are now more commonly used. These include olanzapine risperidone and quetiapine. They are usually better tolerated with fewer extrapyramidal side-effects (such as unacceptable levels of rigidity and dystonia) and a lower incidence of tardive dyskinesia than the older neuroleptics.
The atypical neuroleptics also promote weight gain, suppress irritability, and mood swings, and improve sleep—all of which are useful side-effects in HD. They should be started at the lowest dose, and can be gradually titrated up as needed. Olanzapine and risperidone can both cause hypercholesterolaemia and hyperlipidaemia and are associated with an increased risk of stroke in elderly patients with dementia (Ballard and Howard, 2006); it is therefore important to consider a history of stroke or transient ischemic attack in older patients before using them and to monitor glucose and lipid levels during treatment.

The typical neuroleptics are also still used to suppress chorea. Sulpiride, for example, is a good suppressor of chorea, but can cause agitation and Parkinsonism. Haloperidol causes even more frequent Parkinsonian side effects, and also causes tardive dyskinesia. All neuroleptics carry a risk of neuroleptic malignant syndrome, but this is greater with the typical than the atypical neuroleptics. (Neuroleptic malignant syndrome is a rare, but life-threatening reaction characterized by acute onset of delirium, rigidity, and fever, often accompanied by leukocytosis and elevated CPK. Families should know about this so that patients can be given prompt medication attention if this develops.)

Benzodiazepines can also be used for treatment of chorea, but they cause sedation and can have depressant effects on cognition. For these reasons, they are better avoided in the longer term. Amantadine can also be used for intractable chorea. Its main side-effects are ankle edema, worsening of confusion, and livedo reticularis.

2. Dystonia, spasticity, rigidity, and bradykinesia

As mentioned earlier, rigidity, spasticity and bradykinesia tend to emerge later in adult-onset HD, often becoming more prominent as chorea declines. In juvenile HD, however, a more Parkinsonian phenotype is often present from the onset of the disease. These symptoms usually cause marked functional impairment and often impair gait, leading to falls and the need for a wheelchair.

Dystonia may be a symptom of HD, or a side effect of a neuroleptic. Different presentations include twisting, tilting, or turning of the neck (torticollis), involuntary arching of the back (opisthotonos), and arching of the feet.

A variety of medications have been used to treat rigidity, spasticity, and dystonia. As with chorea, these do not obliterate symptoms, but may partially suppress them. Benzodiazepines or baclofen may relieve stiffness, but may also increase bradykinesia. Anti-Parkinsonian medicines such as levodopa-containing compounds or amantadine can also be helpful. Tizanidine sometimes improves spasticity. All of these medicines may cause delirium, however, and even if initially helpful, may lose their efficacy after several months; improving mobility with the help of a physiotherapist and preventing contractures is frequently the most important aspect of management. Botulinum toxin injections are not often used.
but may be useful if severe rigidity of a particular small muscle or group of muscles is impairing function.

3. Myoclonus and tics

Myoclonus is sudden brief jerking of groups of muscles. It is most common in juvenile-onset HD, and may be mistaken for a seizure. It may not be especially disabling or distressing, but if needed, can be dampened down with clonazepam, sodium valporate, or levetiracetam. Tics are brief, intermittent stereotyped movements such as blinking, nose twitching, head jerking, or transient abnormal postures. Tics can also cause sounds like sniffs, snorts, grunts, coughs, and sucking through involvement of respiratory and vocal structures. As with chorea, patients often do not notice their tics although other people who spend a lot of time with them can find the constant noise of a persistent vocal tic irritating; it is important to explain that, just like chorea, tics are not something that patients can control. Tics do not usually need treatment, but neuroleptics, benzodiazepines, or SSRIs may help to suppress them.

4. Akathisia

Akathisia is an extremely uncomfortable internal sense of restlessness, which may cause patients to pace or to be unable to sit still. It can be caused by neuroleptics and can look like agitation or anxiety; this means that a vicious circle can be created if the causative neuroleptic is increased to treat perceived agitation or anxiety.

B. THE COGNITIVE DISORDER

Cognitive symptoms tend to begin insidiously, but can have a profound effect even at an early stage. In 1993, Rothlind et al. assessed the effect of cognitive and motor symptoms on the ability of 67 individuals with early HD to carry out activities of daily living and found that cognitive impairment was associated with reduced functional ability independent of motor impairment (Rothlind et al., 1993). Additionally, many patients and their families can identify problems at work and in personal relationships that can, with hindsight, be attributed to development of the cognitive syndrome many years before the onset of motor symptoms. Patients themselves may not be aware of these symptoms (or may be in denial about them), and this lack of insight may confound the problem.

The first step in managing cognitive symptoms is therefore to identify areas of difficulty and to recognize that they might be due to HD. This can be difficult to address in at-risk individuals who do not wish to know their gene status and needs
to be introduced gently. There are no pharmacological treatments for cognitive symptoms, but coping strategies can often be adopted to overcome or compensate for problems. Encouraging patients to continue to exercise their mind, for example by doing crosswords or other puzzles, is advised across the disease span, and cognitive behavioral therapy (CBT) can be very helpful for people with early cognitive or behavioral symptoms who have insight and are motivated to engage with the therapy. This can also be a useful way for premanifest individuals to learn cognitive strategies that will stand them in good stead once cognitive and psychiatric symptoms become manifest. (We are aware of no controlled trials of CBT in HD, though one case study has reported benefit for a premanifest individual who underwent CBT to manage depression and anxiety after a positive predictive gene test (Silver, 2003)).

The following sections summarize some of the features of the cognitive syndrome.

1. **Executive dysfunction**

   Executive functions are the high-level cognitive processes that control other aspects of cognitive function. These almost invariably decline in HD. Typically, patients report difficulty with multi-tasking and concentration. Thinking-style becomes more concrete and less efficient, and planning, initiation and organization of time, thoughts and activities become harder. External structure can be provided through establishing regular routines and keeping diaries and “to do” lists; this helps patients to organize activities.

   Difficulty with multitasking is a common early sign of HD, and can result in significant problems in day-to-day function. Many workplaces require rapid switching of attention, for example; HD-related deficits can result in patients making mistakes in this type of environment. Concentrating in a busy office becomes harder and tension develops in relationships with colleagues. This, in turn, increases stress and exacerbates the underlying problem with concentration. Once these issues have been identified, however, appropriate compensatory strategies can be devised. Moving into a quiet office and reducing workload, for example, may enable someone to stay in work and preserve their independence for as long as possible. Employers have a statutory duty to optimize the working environment for people with a disability where possible, though this needs to be approached sensitively and support and advice offered (Novak and Tabrizi, 2010).

2. **Psychomotor symptoms**

   People with HD are frequently impulsive and develop psychomotor perseveration.
3. **Visuospatial and perceptual deficits**

HD causes subtle visuospatial perceptual changes (Craufurd and Snowden, in press; Paulsen *et al.*, 2008). In particular, patients’ perception of their own bodies in relation to the rest of the world can be impaired; this may contribute to trips, falls and bumping into furniture.

4. **Learning and memory**

Memory loss and difficulty in learning new skills are common. Strategies to deal with this include providing cues to jog the memory, and again, keeping “to do” lists and diaries and maintaining regular routines.

5. **Dementia in Huntington’s Disease**

As cognitive dysfunction progresses, patients can develop severely limiting frontal and subcortical dementia. It is important to remember, however, that some people with profound motor symptoms will remain able to comprehend and evaluate information and make decisions for themselves, even if they find this difficult to communicate. Assessment by a clinical psychologist can be extremely helpful in order to explore this more fully and to evaluate the extent of an individual’s capacity.

C. **The Psychiatric Disorder**

Psychiatric symptoms are common in HD and, like cognitive symptoms, often precede motor onset by many years. They frequently lead to considerable distress and difficulty for patients and their families/carers, who typically find them more difficult to deal with than the physical symptoms. It is important to recognize psychiatric symptoms so that symptomatic treatment can be offered, and to acknowledge that symptoms are probably caused by HD. Detection of psychiatric symptoms may be difficult later in the disease as diagnoses may be obscured by other symptoms; 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 misattributed to depression (Novak and Tabrizi, 2010).

HD can cause a wide range of psychiatric symptoms. A survey of 52 patients with HD was found to have symptoms with the frequencies shown in Table III. (Paulsen *et al.*, 2001).

A summary of the pharmacological treatment of psychiatric symptoms in HD is given in Table IV.
1. Depression

Depression is extremely common in HD and occurs as an intrinsic feature of the disease rather than merely as a response to being diagnosed with an incurable disease. A recent survey of 2,835 patients with HD found that 40% currently had symptoms of depression and 50% reported having sought treatment for depression in the past (Paulsen et al., 2005). 10% of those surveyed had made at least one suicide attempt in the past.

Treatment is with standard antidepressant medications. While there is not an established evidence base for the treatment of depression in HD, our experience is that antidepressants are frequently very effective (Novak and Tabrizi, 2010). An SSRI such as citalopram is generally used as first line treatment, though stimulating SSRIs such as fluoxetine should be avoided as they can cause hyperstimulation and exacerbate anxiety, both of which are common in HD. If insomnia is a problem, a sedating antidepressant at night instead (e.g. mirtazapine) can be useful. Psychological therapies, such as CBT, can also be helpful in well-selected patients, and support from local community mental health teams is often invaluable.

2. Suicide risk

Patients with HD are more likely than the general population to commit suicide according to a meta-analysis of studies that reported on mortality associated with mental disorders (standardized mortality ratio of 290) (Harris and Table III

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphoria</td>
<td>69.2</td>
<td>3.12</td>
<td>3.46</td>
</tr>
<tr>
<td>Agitation</td>
<td>67.3</td>
<td>2.88</td>
<td>3.32</td>
</tr>
<tr>
<td>Irritability</td>
<td>65.4</td>
<td>2.63</td>
<td>3.11</td>
</tr>
<tr>
<td>Apathy</td>
<td>55.8</td>
<td>2.79</td>
<td>4.02</td>
</tr>
<tr>
<td>Anxiety</td>
<td>51.9</td>
<td>1.96</td>
<td>3.14</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>34.6</td>
<td>1.29</td>
<td>2.77</td>
</tr>
<tr>
<td>Euphoria</td>
<td>30.8</td>
<td>1.04</td>
<td>2.27</td>
</tr>
<tr>
<td>Delusions</td>
<td>11.5</td>
<td>0.75</td>
<td>2.63</td>
</tr>
<tr>
<td>Aberrant motor</td>
<td>9.6</td>
<td>0.60</td>
<td>2.18</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1.9</td>
<td>0.23</td>
<td>1.66</td>
</tr>
<tr>
<td>Symptom</td>
<td>Drug Class</td>
<td>Medication</td>
<td>Main Adverse Effects and Treatment Notes</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Atypical neuroleptics</td>
<td>Olanzapine, Risperidone, Quetiapine</td>
<td>See above. Careful use in the elderly where there is increased risk of stroke with olanzapine and risperidone</td>
</tr>
<tr>
<td>Treatment-resistant psychosis</td>
<td>Neuroleptics</td>
<td>Clozapine</td>
<td>As for the other neuroleptics, plus agranulocytosis, myocarditis and cardiomyopathy. Requires blood monitoring</td>
</tr>
<tr>
<td>Psychosis with prominent negative symptoms</td>
<td>Neuroleptics</td>
<td>Aripiprazole</td>
<td>Parkinsonism, akathisia, drowsiness, GI disturbance, tremor, blurred vision</td>
</tr>
<tr>
<td>Depression, anxiety, OCB, irritability,</td>
<td>Selective serotonin</td>
<td>Citalopram</td>
<td>GI disturbance, hypersensitivity reactions, drowsiness, syndrome of inappropriate antidiuretic hormone secretion (SIADH), postural hypotension</td>
</tr>
<tr>
<td>aggression</td>
<td>reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(SSRI)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability, aggression</td>
<td>Neuroleptics</td>
<td>Olanzapine, Risperidone, Quetiapine</td>
<td>See above</td>
</tr>
<tr>
<td>Altered sleep-wake cycle</td>
<td>Hypnotics</td>
<td>Zopiclone Zolpidem</td>
<td>Drowsiness, confusion, memory disturbance, GI disturbance See above</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Anticonvulsants</td>
<td>Sodium valproate, Lamotrigine</td>
<td>Hypersensitivity reactions, blood dyscrasias, dizziness, GI disturbance, depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
<td>Hypersensitivity reactions, drowsiness, blood dyscrasias, hepatitis, hyponatremia, dizziness, GI disturbance</td>
</tr>
</tbody>
</table>

Table IV

**Symptomatic Management of Psychiatric Symptoms in Huntington’s Disease** (reproduced from “Huntington’s Disease” by MJU Novak and SJ Tabrizi by kind permission of the publisher).
Barraclough, 1997). A survey of 4,171 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 (Paulsen et al., 2005). It is therefore vital to ask depressed patients whether they have been experiencing suicidal thoughts. Suicidal ideation was highest among (a) gene carriers who were nearing the threshold of being diagnosed with manifest disease (i.e. those with soft motor signs of HD) and (b) among those who were beginning to lose their functional ability and independence (i.e. those with stage 2 disease). Risk factors for suicide in HD include depression and impulsivity (Craufurd and Snowden, in press). Some people with HD also have suicidal thoughts in the absence of depression (Lipe et al., 1993): for some, thoughts of suicide appear to be a rational response to their imminent loss of independence (Novak and Tabrizi, 2010).

3. Anxiety

Anxiety is also common in HD but can respond to treatment with nonstimulating SSRIIs, buspirone or benzodiazepines.

4. Irritability and agitation

As seen in Table III, these are also common symptoms of HD. Both respond well to neuroleptics - olanzapine, for example, is very effective and, as described earlier, has beneficial side-effects. Behavioral strategies are also invaluable and carers should be encouraged to create a calm and structured environment and to avoid confrontation wherever possible. It is also helpful to avoid situations that trigger outbursts, but if this is not possible, short-term use of benzodiazepines (e.g. a low dose of clonazepam) can be useful to reduce agitation and anxiety. These strategies can be difficult for carers to maintain, and support groups like local Huntington’s Disease Association (HDA) meetings can be valuable sources of support and suggestions.

5. Apathy

Apathy is also a challenging symptom to manage. It can be difficult to differentiate from depression and a trial of antidepressants may be worth considering if there is uncertainty about this. It is helpful to gently impose structure on the day as patients often find that having an appointment to aim for, such as coffee with a friend, is a helpful way to initiate and organize their behavior (Novak and Tabrizi, 2010). Patients suffering from apathy can find it particularly difficult to initiate activities, but are often able to participate fully with encouragement and support once they get started on things.
6. **Obsessive-compulsive behaviors and perseveration**

Obsessive-compulsive thoughts and behaviors are also relatively common in HD (Cummings and Cunningham, 1992; Paulsen et al., 2001; Rosenblatt and Leroi, 2000). These take three main forms: obsessions related to other people (e.g. suspicions of infidelity), obsessions which are related to the self (e.g. fixations on bowel or bladder function), and ritualistic behaviors (e.g. preoccupations with specific routines) (Tabrizi et al., 2011). It is generally not helpful to be confrontational; gentle redirection can however be helpful. Neuroleptics such as olanzapine can also improve symptoms, as can antidepressants. The choice of drug class should be based on the pattern of concurrent symptoms: neuroleptics would be a good choice in a patient who also has agitation, for example. In patients with little or no cognitive impairment, CBT can also be useful.

7. **Sexuality**

Sexuality often remains unchanged in HD, though it is also common for sex drive to decline. A minority of people with HD, almost invariably men, develop hypersexuality. An open and supportive atmosphere is important to explore strategies to deal with this. In general, a behavioral approach is used to broach issues arising from altered sexuality, but neuroleptics such as olanzapine can help to reduce hypersexuality if needed. It is also important to remember that many patients with HD are on medications such as SSRIs which can cause sexual dysfunction; these should be reviewed if sexual dysfunction is a problem.

8. **Psychosis**

Psychotic symptoms are rare in HD, but delusions and hallucinations can occur (Paulsen et al., 2001; Rosenblatt and Leroi, 2000). Any precipitating factors should be assessed and treated if present, and neuroleptic treatment instigated as necessary. The choice of specific neuroleptic depends on the concurrent symptom profile (Rosenblatt and Leroi, 2000).

D. **Communication**

Communication can be impaired by both dysarthria and cognitive dysfunction. Dysarthria is mainly caused by incoordination of voluntary oromotor muscle movement and, as with most other HD symptoms, is often worse when an affected individual is tired or under stress. Cognitive symptoms which contribute to communication problems include word-finding difficulties and an inability to initiate or structure speech.
Maintaining communication is vital, and there are a number of strategies which can help to optimize communication. When giving information to someone with HD, it is important to be clear. Decision-making can be challenging, so present an individual with simple and clear choices rather than asking open-ended questions (“would you like a sandwich or a biscuit?” rather than “what would you like to eat?”). Use uncomplicated language and allow the patient plenty of time to reply. Prompting can be helpful to overcome difficulties in initiating speech. People with HD are often distracted by extraneous information in their environment, so if communication is difficult, it can help to move to a quieter space where distractions are minimized. If the listener cannot understand the person with HD, asking them to repeat things or phrasing questions differently may help. As communication problems progress, speech aids such as communication boards can be helpful. People with HD frequently often understand far more than initial attempts at communication suggest, however; it is important to keep this in mind and to look actively for ways to optimize communication.

Speech and language therapy (SALT) is frequently helpful and can be very useful to maximize speech clarity in the early stages of the disease and to teach patients and their families communication strategies while they have the cognitive ability to learn them.

### E. Swallowing Problems

Swallowing problems also arise from both motor and cognitive dysfunction. Oromotor incoordination and distractibility are common factors. Food often goes down the wrong way when patients are distracted while eating; minimizing distractions such as talking or watching television during mealtimes is helpful and patients should be advised to eat slowly, sitting upright and concentrating on chewing and swallowing. Meals may need to be supervised with carers reinforcing this advice, and it is important to make sure that any dentures fit well. As the disease progresses, people with HD usually need to modify their diets to avoid troublesome foods, and food consistencies can be altered to reduce the chance of aspiration, for example by adding thickener to fluids. SALT referral is important at an early stage for advice on how to reduce the risk of aspiration and it is useful for carers to be trained in how to perform airway clearing maneuvers in case choking occurs.

Eventually patients may become unable to swallow anything safely and PEG insertion may be considered. This is often a highly emotive subject and the issue should be raised with patients and their carers while patients are still able to eat to avoid crisis point being reached. PEG insertion does reduce the risk of aspiration but patients may choose not to have this. It may be the subject that triggers a patient to make an advanced directive; a significant number of individuals decide against PEG insertion and planning in advance with an advanced directive can be invaluable in
avoiding the need to discuss this when disease has advanced to the point when patients are unable to communicate and a decision is needed urgently. This is discussed in more detail in the section on advanced disease and end of life issues.

F. Nutrition

Widespread metabolic and endocrine changes are increasingly recognized in HD, and their management can be difficult. The disease creates a catabolic state, resulting in weight loss being a prominent feature of HD. This may begin in the prodromal period of the disease. As the disease progresses, massive weight loss may occur unless calorie intake is increased. People with HD often need a vastly increased daily calorie intake—up to 4000 calories a day—to maintain a stable weight. Anecdotally, weight loss has a negative impact on other symptoms, so avoiding it and monitoring weight carefully is a priority.

Diet can be supplemented with high calorie foods such as cream and chocolate in the first instance. Nutritional supplements are useful as the disease progresses, and referral to a dietician to optimize calorie intake while maintaining as well balanced and enjoyable a diet as possible can be helpful. As people with HD are encouraged to eat a high calorie/high sugar diet, close attention should be paid to oral hygiene and regular dental reviews encouraged.

G. Sleep

Sleep disturbance is common in HD (Arnulf et al., 2008; Hansotia et al., 1985; Videnovic et al., 2009; Wiegand et al., 1991). Low mood, anxiety, and added movements are all secondary causes of insomnia, and in addition, primary sleep disturbance is a significant feature of the disease itself. The sleep-wake cycle becomes disordered and daytime somnolence is common.

Sleep hygiene measures are the first step in managing this; avoiding afternoon napping and keeping regular hours for going to bed and getting up are particularly important things to mention to patients, especially as the cognitive changes of HD mean that they can find it difficult to impose structure on daily routines. Treating chorea and mood disturbances as required can improve sleep, and a small dose of olanzapine or clonazepam at night as sedation may also be helpful.

H. Metabolic and Endocrine Features

As mentioned earlier, widespread metabolic and endocrine changes are increasingly recognized in HD. Weight loss and sleep disturbances have been
mentioned in the sections above. Other metabolic and endocrine effects of HD include cardiac failure, increased peripheral inflammation, and altered endocrine profiles (van der Burg et al., 2009). Neither the pathological mechanisms underlying these nor their impact on the clinical manifestations of the disease are yet fully understood; they are the subject of increasing research interest.

I. SEIZURES

Seizures are common in juvenile HD; they are seen in 30–50% of cases (Brackenridge, 1980; Hayden, 1981; Jervis, 1963; Kremer, in press; Osborne et al., 1982). This is in contrast with adult onset HD, in which the incidence of seizures is similar to that of the general population: approximately 1-3% (Hayden, 1981).

A first seizure should not be attributed to HD without further evaluation as it may be indicative of an additional neurological problem, such as a subdural hematoma sustained in a fall. The workup of a first seizure should include a complete examination, laboratory studies to rule out an infection or metabolic disturbance, an EEG, and a brain imaging study. The treatment of a seizure disorder in a person with HD depends on the seizure type. In patients with juvenile HD, myoclonic epilepsy or other generalized seizures are usually treated initially with sodium valproate. Although seizure management in HD is not usually particularly problematic, seizure control can be difficult in some cases and may require a combination of drugs or referral to a specialist.

III. The Atypical Phenotype, including Juvenile Huntington’s Disease

Although the majority of people with HD have the typical hyperkinetic phenotype with symptom onset in adulthood, variant phenotypes exist. Juvenile Huntington’s Disease (JHD) is HD which manifests in people before they are 20 years old, and is typically associated with a CAG repeat length of greater than 50. Andrew et al. (1993), for example, found that CAG repeat length ranged from 46 to 121 with a median repeat length of 56.5 in a sample of 20 juvenile HD patients. Juvenile HD causes many of the same symptoms as adult-onset disease although the movement disorder is typically hypokinetic rather than hyperkinetic. The presentation of juvenile HD is therefore similar to young-onset Parkinson’s disease and levodopa is often used as symptomatic treatment. The rigid variant of HD is also known as Parkinsohnian, akinetic-rigid, or Westphal variant HD, and though it is usually seen in young-onset HD, it can also occur in adults. The overall incidence of this phenotype is around 6–10% of all HD cases (Shoulson and Chase, 1975).
Late onset HD is also well recognized; this is when manifest disease does not develop until an individual is over 60 years old. On average, late onset HD follows a more benign course than typical onset HD, with slower disease progression and, frequently, milder symptoms (Kremer, in press).

### IV. Advanced Disease and End of Life Issues

Patients with advanced HD require significant support in all activities of daily living, usually because of a combination of motor, cognitive, and behavioral symptoms. Communication may be severely limited and muteness is common, often resulting in agitation and frustration due to inability to speak. HD does not cause a global dementia, however, and the ability to recognize and interact with people is frequently relatively well preserved.

As HD progresses, it often becomes increasingly difficult to provide care at home. Looking after someone with advanced HD at home is challenging and frequently exhausting, and carers should be offered considerable levels of support, including periods of respite care. For many people, however, a nursing home is the best option; education and support should be provided for staff to facilitate understanding of the complexity of caring for someone with HD. Periods of respite during which the patient spends time in a nursing home can be a useful way for the patient and his or family to develop a relationship with the nursing home staff; this can ease the transition to full time nursing home residency at a later stage, avoiding or reducing the agitation caused by moving someone with advanced disease directly into an entirely new environment. Involvement of palliative care teams in addition to HD teams can be extremely helpful when managing advanced HD.

As cognitive impairment progresses, patients with HD almost invariably lose the capacity to make decisions about their own care. It is therefore helpful to raise potentially problematic questions early in the course of the disease to allow individuals to plan ahead while they still have the cognitive capacity to do so. Given that people with HD have usually seen the progression of the disease in other family members, bringing up the issues surrounding end of life care rarely comes out of the blue. Topics that commonly arise include:

1. **Advanced Decisions to Refuse Treatment** (previously known as advanced directives): these are extremely helpful and allow individuals to make decisions about their care in advance. 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.
2. **Power of Attorney**: this allows an individual to nominate someone else to make decisions on their behalf.

3. **Enteral feeding** (usually via percutaneous endoscopic gastrostomy, or PEG): this may be appropriate in patients who are unable to maintain adequate nutrition and body weight.

4. **Use of antibiotics or intravenous fluids** in an individual with end stage disease.

The most common causes of death in people with HD are bronchopneumonia and heart disease, with choking, nutritional deficiencies, and chronic skin ulcers also associated with mortality (Lanska et al., 1988a, 1988b; Sorensen and Fenger, 1992). In our experience, few patients request information about assisted suicide. This remains illegal in the UK.

V. **Looking to the Future: Research into New Treatments for Huntington’s Disease**

At the time of writing, there is a major drive to find disease-modifying and new symptomatic treatments for HD; many new developments have been made in recent years, and phase 3 trials are ongoing (Novak and Tabrizi, 2010). Much progress has also been made in developing and evaluating sensitive biomarkers which will help to measure the effects of disease modifying therapies in future clinical trials, particularly in the premanifest and early stages of the disease (Paulsen et al., 2008; Tabrizi et al., 2009).

Future disease modifying treatments will, in practice, probably comprise a combination of compounds which will target several key pathogenic pathways to achieve optimal effect. This approach is similar to that used in the treatment of HIV or cancer. Some potential therapeutic strategies are summarized below (Ross and Tabrizi, 2011).

- Enhancing clearance of mutant huntingtin by cellular clearance mechanisms: a number of compounds being tested in mouse models of HD aim to promote clearance of the mutant protein, huntingtin, which is generated by the expanded \( \text{HTT} \) gene.
- Histone deacetylase inhibitors: these target the transcriptional dysregulation that occurs early in HD pathogenesis.
- Inhibitors of proteolytic cleavage of full-length mutant huntingtin to prevent production of the potentially toxic N-terminal fragment.
- Gene silencing: switching off expression of the mutant gene itself.

VI. **Conclusions**

HD is a multisystem disease that is characterized primarily by progressive motor, cognitive, and psychiatric symptoms. Management of the disease is
challenging, but there are many options which can ameliorate symptoms and improve quality of life; these are best provided in a collaborative multidisciplinary setting. Extensive research is currently being carried out with the aim of developing treatments that will delay or halt the disease process in the premanifest phase.

References


