REVIEW

The management of Huntington's

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Clinical guidelines are systematically developed statements to help doctors and their colleagues make decisions about appropriate health care for specific disorders. Such guidelines ought to be properly based on published peer reviewed practice. However, there is little of this sort of help in Huntington's disease, although the literature base is growing. This paper does not attempt to be definitive, rather it presents a method of management which has evolved to match the needs of patients as they emerge, and which as far as is possible, is in accord with the evidence available at present.

HISTORY

In 1872, at a medical meeting in Ohio, USA, George Huntington (Huntingdon 1872) described the disease which later came to bear his name. He was a young general practitioner who worked in his father's practice, as had his father's father before that. They therefore had known several generations of some families and had recognised the familial nature of the choreiform movement disorder, which the families called 'that disease'. Huntington concluded his talk by saying that he knew nothing of its pathology and, 130 years later, little in that sense has changed. Although we now know the genetic basis of the disease, we do not understand the mechanism of the disease, but clues are accumulating rapidly. The advent of the presymptomatic predictive test has not lead to any decline of the disease as some had hoped (Tyler *et al*. 1992) and others predicted (Martindale & Bottomley 1980), and the suffering of the families continues.

GENETICS

Huntington's disease is a neurodegenerative disorder inherited as an autosomal dominant trait (Fig. 1). Men and women are affected equally, and males or females can transmit the disorder to their sons and daughters, each of whom has their own independent 50% risk of inheriting the responsible mutation. The disease is fully penetrant, if you inherit the mutated gene you will develop the disorder. If you do not inherit

disease

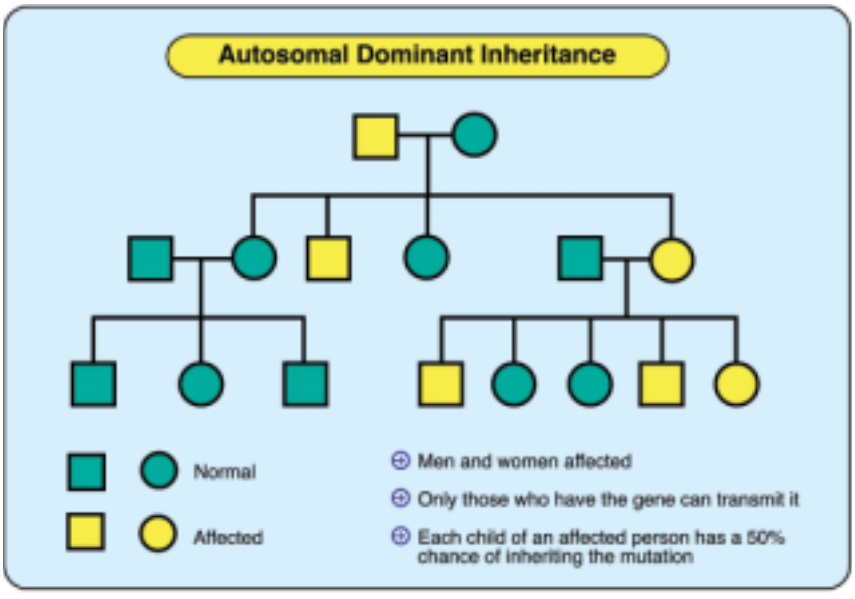

Figure 1 A family tree to illustrate autosomal dominant inheritance.

the mutated gene, you cannot pass it to any of your children.

Huntington's disease has a prevalence of about 1/10 000 worldwide, though some countries such as Finland and Japan appear to have lower numbers affected (Bates 2002). For every affected individual there are at least four other people at 50% risk, assuming there are siblings and offspring, with all the concomitant difficulties of their uncertain status. In addition, the partners of these people all have their own difficulties – the problems of Huntington's disease are not rare.

The locus of the responsible gene, Huntingtin, is on chromosome 4, and the mutation was identified in 1993 (Huntington's Disease Collaborative Research Group 1993). The polyglutamine expansion (or CAG repeat) is now known to be a common type of mutation in other neurological disorders, such as some of the ataxias. Nowadays, DNA from a peripheral blood sample is all that is needed for diagnosis. More than 36 CAG repeats is diagnostic, and most affected individuals have 40–50 (Fig. 2). Affected children and adolesecents have more than 50 CAG repeats. The smaller mutations (fewer than 40 repeats) are associated with onset at an older age. The disease and the age of onset may vary considerably in and between families, even when the mutation size is identical.

The disease most commonly starts late in the fourth decade, but childhood onset can occur, and onset in the 70s is not unusual (Fig. 3). When a child is affected, most often the disease has been inherited from the father, because an increase in the size of the mutation more often occurs during spermatogenesis than in oogenesis. I have seen an affected 11 year old, whose

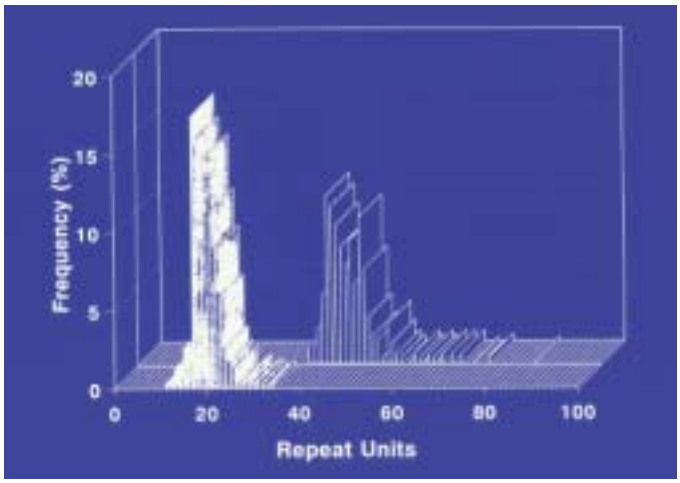

Figure 2 The frequency and range of the CAG repeat in the Grampian Region of Scotland: normals on the left and Huntington's patients on the right.

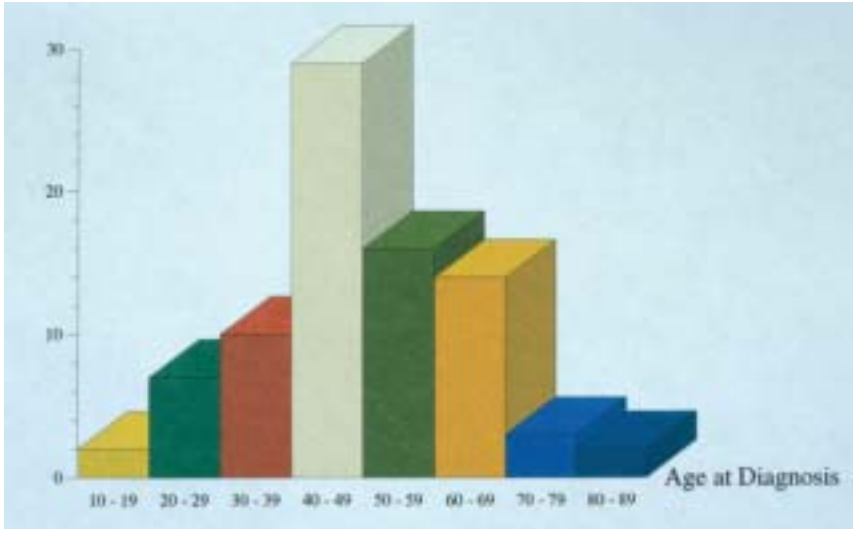

Figure 3 The age range at diagnosis of Huntington's disease in Grampian.

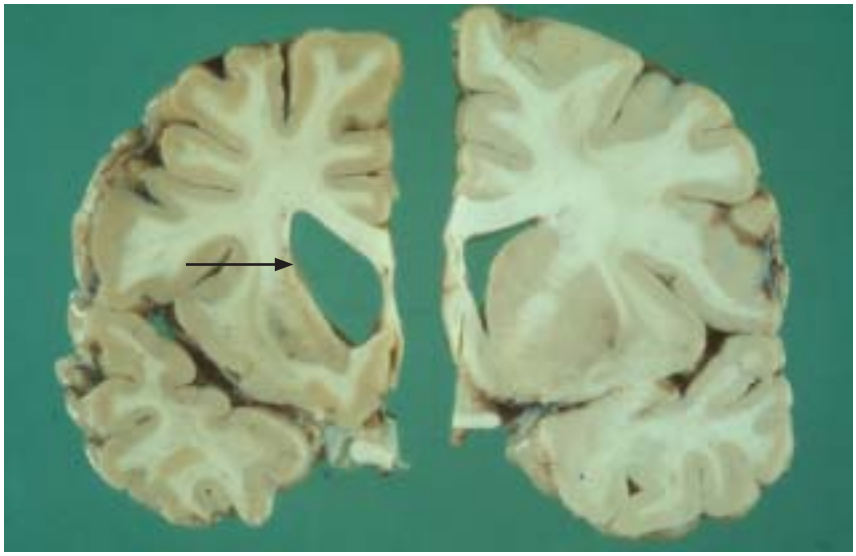

Figure 4 A Huntington's disease brain on the left showing caudate (arrow) and cortical trophy. A normal brain is shown on the right.

father had yet to develop symptoms because his mutation was of average size, yet that of his child was greatly expanded.

PATHOLOGY

The principal areas of neurodegeneration are in the medium spiny neurons of the caudate nucleus, putamen and globus pallidus, as well as frontal cortex (Fig. 4). The pathophysiology of the disease is outwith the scope of this paper, but it is accepted that the mutated protein produces a new function for the gene, and this most likely involves interaction with other proteins, to the detriment of cellular function.

CLINICAL FEATURES

Motor problems

The classical clinical feature is the involuntary choreiform movement disorder, which looks semi-purposeful, but other movements can be seen such as dystonia, athetosis, tics, myoclonus and ballismus. These can increase as the disease advances, other than perhaps tics which are often seen at an early stage. In later stages, additional movements may be less obvious because they are masked by the developing rigidity and bradykinesia. But some patients have very few abnormal movements at any stage. I have seen a patient whose movements disappeared entirely in the late stage, in the absence of marked rigidity or drug therapy.

Impairment of voluntary movement occurs, and this, rather than the choreiform movements, is closely linked to the functional disability of the patient. Delayed initiation of movements and slowed, inaccurate execution of movements are consistently present, and these progress throughout the disease process. Treatment of the choreiform movements with neuroleptics may exacerbate these 'parkinsonian' symptoms, and so contribute to further loss of functional capacity.

Speech problems

Dysarthria is a common early sign. Patients have difficulties in initiation of speech and in articulation – both rate and rhythm are disturbed as laryngeal and respiratory muscles become involved in the movement disorder. These essentially mechanical problems are made worse by cortical and striatal neuronal loss resulting in reduced linguistic ability (Gordon & Illes 1987). Loss of the ability to communicate one's needs is a considerable difficulty for this patient group.

The ill-informed carer often underestimates the cognitive ability of the patient in these circumstances, leading to behavioural problems, and lack of good care. Speech aids should be introduced at an early stage, when the patient can still learn new skills, so that familiarity with the aid can lead to a smooth transition to its use in the future. Keyboards can be difficult to use in the later stages because of the motor difficulties, although they can be useful as an interim measure.

Swallowing problems

In many patients, but not all, incoordinate swallowing may result in episodes of aspiration in mid to late disease. Certainly chest infections are a common source of morbidity, and bronchopneumonia is a frequent terminal event (Simpson 1992). The cause of the dysphagia is complex, but certainly involves disruption of safe swallowing due to buccolingual chorea, and abnormal respiratory control. Uncontrolled tachyphagia is also often present. Difficulties when swallowing liquids are often the first sign of trouble. Thickening liquids can be of great assistance. Cutting food into small pieces can also be helpful, a porridge-like consistency is the best managed. The simple advice to avoid putting two textures in the mouth at the same time can transform mealtimes for patients. Sitting undisturbed in a quiet environment is also helpful.

Adequate nutrition can be difficult to achieve in these circumstances, and it is important to monitor the patient's weight. Frequent feeding, or grazing, and high calorie diets are prescribed. In one study, it was found that >7000 Kcal were required by an affected patient to maintain their weight (More, 1993).

Cognitive problems

Cognitive difficulties are universal, but they are complex and can be subtle, leading to difficulties in management. Visuospatial ability may be impaired and deficits in complex psychomotor tasks may be apparent before the onset of any overt motor symptoms. There is frequently general impairment in processing new information, as well as in retrieving stored knowledge about events from the recent and even remote past. Executive functioning is adversely affected such that planning and initiating activities are significantly impaired. However, patients may have well-preserved general intellectual and language abilities compared to patients with other dementing disorders such as Alzheimer's disease. Socially this can lead to an overestimate of their abilities unless formal neuropsychological testing is done. This overestimate can be a particular difficulty because anosognosia (or lack of self-awareness) is a common phenomenon. In a superficial assessment situation, it is common for the patient to answer 'I'm fine!' to all queries, whilst the carer looks on despairingly.

Personality and psychological problems

Psychological difficulties are also universal. These range from anxiety to conduct disorders and psychoses. Most distressing for the families are the personality changes: irritability, aggression, impaired social judgement and abnormalities of prosody lead to marital difficulties and problems with the children in the home. Depression is a very common presenting feature, but of course is too non-specific to help in early diagnosis (Pflanz *et al*. 1991).

Many patients exhibit obsessive or compulsive symptoms, as can be noted on the Yale–Brown scale (Anderson *et al*. 2001). Patients with these features show significantly greater impairment on neuropsychological tests measuring executive function than those without such symptoms.

DIAGNOSIS

Sensitive management of the families allows involvement of the partner and offspring of the likely affected person when a decision is being made to undertake a diagnostic test. Huntington's disease never affects a single individual. Siblings and offspring may disagree on whether such a diagnostic test should be performed, although in general best management of the patient should recognise the benefits of an accurate diagnosis for the patient and family.

Many neurologists, who have met the clinical geneticist who asks for informed consent from the patient and/or relatives before being able to proceed with diagnostic testing, ask what makes Huntington's different from other diseases in this regard. The reason is that the diagnosis is not an easy one to receive under any circumstance, especially when it has not been diagnosed in the family before. Angry scenes in clinics or hospital wards, and frank denial and disbelief can accompany the diagnosis and the telling of it. Furthermore, the diagnosis of Huntington's disease has profound effects on the offspring of an affected individual. Refusal of insurance, mortgages and even critical life cover are common. Couples are denied the op-

portunity to adopt or foster a child, and individuals can lose their jobs in the armed forces, and other professions. Discussing potential problems before formal testing is helpful but can never remove the dreadful trauma for the affected families.

PRESYMPTOMATIC PREDICTIVE TESTING

Only 15–20% of those at risk for Huntington's disease decide to undergo presymptomatic predictive testing. In the UK (and virtually world-wide) the presymptomatic testing programmes are undertaken almost exclusively by clinical geneticists with a full supporting framework of preparation and counselling (Simpson & Alexander 1995). The international family organisations were involved in the creation of the guidelines (IHA/WFN 1994) and they are regarded as important by support groups, professionals and almost all applicants for testing.

The literature suggests that those who undergo testing have no regrets, despite marital and professional problems (Almqvist *et al*. 1999). There are few examples of self-harm. Data from the UK Prediction Consortium, which has monitored all presymptomatic tests in the UK since testing began 16 years ago, has information on over 5000 completed tests (Harper *et al*. 2000). This has given valuable information on the effects of testing and on clinical practice in the field. Difficulties continue to occur for individuals, as predicted (Simpson & Harding 1993) but the test remains an extraordinary resource for these families (Fig. 5). Those demonstrated to have the mutation for the disease can be offered continuing follow-up and assessment while specialist clinics can offer regular assessment and more general management, along with clinically orientated research, including clinical trials.

Figure 5 Two women from the last century from a Huntington's family long before presymptomatic predictive testing became available. They chose to remain unwed and childless in an effort to control the emergence of the disease in their family. They did not develop the disease. This photograph is used with the permission of their family.

PRENATAL TESTING

Prenatal testing, with the aim of terminating a fetus shown to have the mutation, is not frequently requested in Europe (Simpson *et al*. 2002). Nonetheless, it is an invaluable tool for some couples who may have had many attempts at pregnancy before they conceive a child shown not to have the mutation, so determined are they that their child will be born without any risk of the disease. However, a considerable majority of individuals who are at risk, and those who know they have the mutation, continue to have children, such is their hope for the future (Evers-Kiebooms 2002).

At present, mutation analysis, using fetal tissue obtained by chorion villus biopsy at around 12 weeks gestation, can produce information about the status of the pregnancy within a week, allowing early termination of an affected pregnancy. However, not all those who find their baby carries the mutation will terminate the pregnancy. This inevitably leads to the birth of a child where the parents know with certainty that he or she has inherited the mutation and will develop the disease (Tolmie *et al*. 1995). This creates substantial difficulties for the family, and the child, many of which have still to appear in the literature. The prediction of an adult onset disease in a child, as a result of a parent's wishes for a child who has not been given a choice in the matter, has been debated at length (Clarke *et al*. 1994). This is issue is not unique to Huntington's disease, and continues to cause concern.

EXCLUSION TESTING

Exclusion testing can allow a parent who does not wish to know their own status, to have a child at very low risk of developing the disease. Using polymorphic markers linked to the disease locus, rather than examining for the presence of the mutation itself, the 4 chromosome 4s from the

grandparents can be identified (Fig. 6). The at risk chromosome from the affected parent can then be identified in generation 2. This chromosome gives the parent of the pregnancy their 50% risk. Using chorion villus sampling, its transmission to the fetus, or not, can be ascertained. If this grandparental chromosome is passed to the fetus then it shares the same risk as the parent (50%). If not, then the fetus is not at risk although there is a risk of recombination. As we do not know if the chromosome from the affected grandparent that has been passed to the parent in generation 2 has the mutation (there is simply a 50% risk), then no additional information will have been produced for the parent. However, in this test fetuses will be aborted who are free of the mutation; i.e. those whose parent lives on to an old age without showing evidence of the disease. But this is a risk these parents are prepared to take, in order to remain ignorant of their own status.

MANAGEMENT

It is easy to understand the difficulties providing long term management for any progressive incurable disease when one looks at the financial demands made upon the health service, and the budgets of those who provide care in the community. With the catalogue of problems in Huntington's disease, one can see why colleagues have, in the past, written off patients in letters to general practitioners after the diagnosis, *'This man has Huntington's disease, there is nothing more that I can do'*. But, although the disease is presently incurable, there is much that one *can* do to improve the quality of life for patients and their families. I would argue that this in turn can help reduce expensive crisis management and inappropriate care provision for the affected person.

The family

Managing the patients' clinical problems is only one aspect of the provision of care. The patient is generally not alone – he or she may have a partner, children, siblings and an employer. The morbidity of these groups is substantial but only just beginning to be documented (Semper, 2000, Forrest *et al*. 2004). These issues must be addressed if management of the affected person is to be successful.

The provision of general information about the disease and its progression is an important part of the work of a specialist clinic. Access to voluntary groups, whose user-friendly literature provides details a clinician may not have, can greatly aid a family in understanding what lies ahead. These groups – for example, the Scottish Huntington's Association and the Huntington's Disease Association in England – provide the opportunity for families to meet and share experiences. To some families who think they are alone with their disease this can be a lifeline. The Scottish Huntington's Association initiative of securing a youth worker for the young people of the families is also an important step because they are frequently left out of the information loop (Forrest *et al*. 2004) and may be misinformed about the condition and their risks as a result. This can lead to school refusal, drug and alcohol abuse, and isolation from the family.

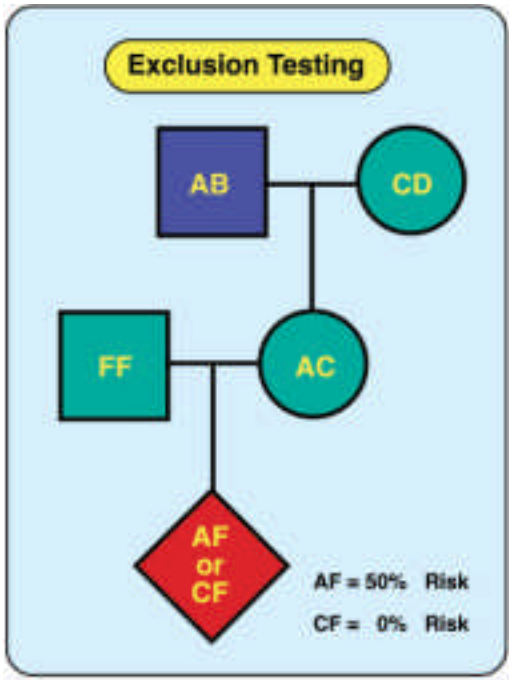

Figure 6 Exclusion testing for Huntington's disease in pregnancy: the fetus has either a 50% risk or no risk at all, depending on whether it inherits A or C from the mother.

Assessment of the patient

Informed management requires knowledge of the patient. A detailed clinical examination must record the motor features, and also document any behavioural changes, cognitive decline, the status of speech and swallowing and the chest, as well as the social circumstances. All this is necessary before one can give advice about safety within the home, or the need for others to be involved in daily care. Information should always include contributions from the partner or carer. The anosognosia described above will often lead to the standard reply of 'I'm fine!' to the enquiry of 'How are you?' and this from someone who has staggered into the clinic, bumping against walls and furniture, much to the discomfiture of the nursing staff.

An objective assessment of the clinical findings in patients with Huntington's disease is also necessary for an evaluation of the longitudinal progression. The Unified Huntington's Disease Rating Scale (UHDRS) was developed to assess four domains of clinical performance and capacity: motor function, cognitive function, behavioural abnormalities, and functional capacity (Siesling *et al*. 1998). Annual evaluation in every patient gives a clear description of the progression of the disease, and can be used to determine the need for appropriate and timely therapeutic intervention.

Neuropsychological examination is an essential assessment tool. This describes cognitive

although the disease is presently incurable, there is much that one *can* do to improve the quality of life for patients and their families

status as well as revealing the extent of the very specific cognitive impairments of the disease. Characteristically, diminished concentration and attention are evident, as well as poor planning and impaired executive functioning. Poor short-term memory is usually demonstrated and, in particular, impairment of episodic memory can be found. Lack of appropriate assessment tools can create false impressions. The Digit Symbol on the Weschler intelligence scale can lead to an inappropriately low score of processing speed if the patient's voluntary motor skills are impaired. Similarly, measures of visuospatial skills and executive functioning, such as constructional drawing and Wisconsin card sorting, can give misleading results. A patient who is dysarthric, or whose responses are delayed, as is often the case, will have difficulty showing their true skills. It is important to be sensitive to the features described above, so that a realistic picture of the patient emerges.

Speech and language assessment allows planning for what may lie ahead. We have shown that the provision of speech therapy can allow retention of clear speech for longer. In addition, a swallowing assessment using videofluoroscopy can detail any difficulties the patient may have. Uncoordinated swallowing leads to aspiration, and bronchopneumonia is a common cause of death.

Social and financial issues

This disease usually strikes at an age when an individual has the greatest responsibility to family and work. It is, therefore, important that the family receive the benefits to which they are entitled. This is a minefield for the uninitiated, and the services of the patient organisations and social work care managers are much appreciated by my patients, and me. It is important to bear in the mind the anosognosia under these circumstances. The inexperienced assessor for benefits may well be convinced by the mobile Huntington's patient who answers 'I'm fine' to all questions into thinking that they do not qualify for support. In fact they may not be safe to be out alone for fear of falls or inappropriate behaviour such as stepping in front of cars as they walk across streets without due care. Support by well-informed individuals is essential in these circumstances.

I raise the issue of creation of power of attorney early in the disease process. This allows the patient to make their own decisions about who they wish to be put in charge of their affairs as the disease progresses. This is a sensitive issue, but these patients know what lies ahead, because they have usually lived with a parent or sibling with the disease. Lack of planning can lead to difficulties with family finances for the surviving partner or other family members. This is especially important if the cognitively and emotionally impaired affected individual decides, for example, that he is now able to live alone and demands that his wife and children move elsewhere, uses his benefits and allowances for himself, and ignores the plight of his family. Unless the patient's cognitive status has been previously defined it can be very difficult to use the legal process to help families in this situation.

Drug therapy

Depression is common and often under-diagnosed because the patient and their family fail to correctly interpret the symptoms.

THE COMPLICATIONS OF HUNTINGTON'S DISEASE TO BE AWARE OF, AS WELL AS THE ABNORMAL MOVEMENTS AND COGNITIVE DECLINE

- Depression, anxiety, irritability, aggression.
- Swallowing problems, aspiration and malnutrition.
- Dysarthria and communication problems.
- Rigidity, bradykinesia and impaired voluntary movements.
- Anosognosia.

It is one of the complications that can be rewarding to treat, because the patient generally responds well. Irritability is common, and can feature early in the disease as a component of the personality changes that the partner sees developing. It can also accompany signs of depression. Both these features can be dramatically improved with the use of some antidepressants such as a serotonin reuptake inhibitor. This is one drug where both patient and carer are often dramatically grateful for its prescription.

Aggression may be closely related to irritability and depression. It can also be a response to an environment that the patient is no longer able to comprehend or control. With this in mind, it is important that the patient's circumstances are investigated, and a cause found for their difficulties before sedative or antipsychotic drugs are administered. This becomes especially important when the patient's speech is impaired, and they can no longer easily communicate their needs. The use of the neuroleptic haloperidol can be useful in this circumstance, especially since it can also serve to modify the movement disorder. Relatively small doses of 0.5 mg twice daily can be effective, considerably less than the larger antipsychotic doses required in a psychiatric setting. Sulpiride is also well tolerated in doses of 200–400mg daily.

The abnormal movements are often surprisingly well tolerated by these patients. Indeed it is often the patient's family who make a request for treatment because of the social implications of the abnormal and excessive movements. I prescribe when the movements can be seen to contribute to weight loss, or are disabling, not earlier because the Huntington's patient is particularly vulnerable to the effects of medication such as the neuroleptics. These can be especially sedative, and long-term use can lead to disabling dystonia. In addition, gait problems and swallowing difficulties can be made worse. Furthermore, movements can lessen with disease progression, and in some of my patients they

have subsided dramatically in late disease so that the medications can be stopped. Despite this, the neuroleptics such as tetrabenazine and sulpiride remain very useful drugs. It is important to start with a low dose, and to slowly increase according to therapeutic response and any adverse effects. I start tetrabenazine at 12.5mg at night, and increase to 12.5mg bd after a week, rarely going above 50mg a day. Later in the disease the benzodiazepine clonazepam can be very helpful, although sedating, even at doses of 1mg bd.

The stiffness and dystonia later in the disease can respond to baclofen, starting with 5mg tds.

Assessment and help for physical disability are important. Wheelchair use is helpful, when out of doors, especially for safe mobility in the later stages of the disease, even though the patient can still walk, and indeed should be encouraged to do so wherever possible. Head injury is an important cause of death in these patients, but simple measures such as wheelchair use can reduce this risk.

Advice about safe swallowing should include discussion about the use of correctly fitting, and secured, dentures and dental plates. Otherwise they can be aspirated.

The provision of an adequate calorie intake is essential but fraught, because the patients eat slowly and with difficulty. High calorie foods are used with effect. Per gastrostomy feeding is used in some cases, but there are ethical issues to consider in late disease.

The multidisciplinary clinic serves this patient group well (Has 1996). These patients rarely conform to the textbook description, and require the availability of unique regimes tailored to their individual needs provided by those well informed in the disease process.

PRACTICE POINTS

- Huntington's disease is a disease of families, not just affected individuals.
- It affects all ages.
- It is variable within and between families: there is no *typical* case.
- There is a mutation unique to Huntington's: diagnosis and prediction are accurate.
- Prenatal tests can provide information about a fetus but need not provide additional information for the parent.
- The abnormal movements need not necessarily be treated.
- The families wish to be involved in decision making about care, especially end of life issues.

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