Ethical aspects of plans to combat Huntington's disease

C J Brackenridge *Department of Psychiatry, University of Melbourne, Victoria, Australia*

Author's abstract

Consideration is given to some strategies to combat Huntington's disease in the absence of treatment to arrest its progress. Ethical issues for tests such as levodopa loading, to provoke symptoms prematurely in carriers of the gene, are compared with those associated with schemes for delaying the onset of disease. The major drawback of these designs is the uncertainty that prodromal symptoms may be extended unduly and the severity of deferred symptoms worsened. Some attention is also given to the possible use of post-onset plans to reduce illness severity and prolong survival. It is concluded that the characteristics of persons less prone to undesirable consequences of onset-delay should be adequately investigated before attempting to implement such schedules as a practical measure.

Introduction

Huntington's disease is transmitted in an autosomal dominant manner with complete penetrance and a strikingly low mutation rate, so that an average of one-half of the offspring of an affected parent will be expected to evince signs of the illness in due course. This usually occurs in adult life, often after a carrier of the gene has attained parenthood, and thereby passed on to the next generation the risk of inheritance. There is currently no proven method of determining whether a symptom-free descendant of a patient with the disease bears the gene. Much research is being directed towards devising a test to discriminate between heterozygotes and normal homozygotes. The rationale is that if a difference is found between affected and normal persons, then the same should apply to presymptomatic carriers of the gene.

This assumption may be questioned on two grounds, one theoretical and one practical. It has been suggested (1) that the gene for Huntington's disease may be triggered by some other gene or unknown genetic control mechanism relatively late in life rather than being 'switched on' *in utero*. Also, if quantitative considerations apply, it is plausible that a defect readily measurable in a typically affected patient may be undetectable in a symptom-free person at risk. The latter possibility has been raised by investigators (2) who have proposed the use of levodopa to elicit premature symptoms. The test is based on the observation that

chorea is worsened by levodopa, due possibly to receptor site hypersensitivity to dopamine. Oral administration to subjects at risk has been found to induce involuntary movements in a proportion of those at risk. (3-5).

The point has been made (2) that a negative is less meaningful than a positive result since the receptor sites may not yet be sufficiently altered to elicit chorea. In these circumstances a patient might well show a negative result on one occasion and a positive result at a later date when the necessary degree of intolerance has developed in the striatum.

An entirely different approach to the problem of combatting the disease lies in delaying the age of onset. (6) If the manifestation of signs of the disorder could be deferred to a late age, much of the distress resulting from it would be overcome. Some of the environmental factors promoting onset of symptoms are now being elucidated (7-9) and it is not unrealistic to suppose that, as more extraneous influences are recognised and better understood, a significant degree of control over the time of onset will be achieved.

Like most presymptomatic tests, onset-delay does not require a knowledge of the basic defect of the disorder. The schemes envisaged at this early stage of their development are essentially stress-avoidance measures, since factors promoting the delay of symptoms are poorly, if at all, understood. Most will be initiated in the context of genetic counselling when information will be tendered about adverse lifestyles and situations conducive to bringing on the disease at an avoidably early time. Pregnancy, with its traumas of childbirth or miscarriage for women, (7, 10, 11) and certain forms of occupational stress for men, (9) typify life events and social factors considered to accelerate the onset of symptoms. Another category of extraneous variables are such epidemiological factors as climate, which appears to influence the age at which signs of the disorder occur. (8) In the near future many more onset-precipitating factors will be recognised and better understood, so that onset-delaying schemes will assume the form of multifactorial prescriptions, the composition of which will be adapted to the sex, age and other characteristics of the individual.

Stress reduction is the most important beneficial concept that has arisen from investigations of onset-provoking factors to date. Therapeutic prophylaxis

commends itself as an attractive and more practical measure, although designing tests of pharmacological potency to defer onset would prove difficult. It is at once evident that the allaying effect of such a preventive measure is the converse of the provocative effect of a symptom-precipitating test such as levodopa loading. Because prophylactic deferment is likely to be simpler to implement than stress avoidance, it seems to offer the best avenue of approach to onset-delaying schemes.

Ethical issues in onset-delay

The nature of the disorder, the predicament that no ultimately effective treatment is available and the desire for presymptomatic detection or onset delay raise many ethical questions. Some of these are unique to Huntington's disease while others are shared by various genetic or degenerative neurological disorders. (12) While reference will be made to some of the issues arising from the use of predictive experiments, particularly the levodopa loading test, the main purpose of the present article is to present and discuss the salient problems, both ethical and practical, that stem from onset-delaying schemes. Even though such plans are in their infancy, it would be irresponsible to embark upon them without considering some likely implications of their use.

Onset-delaying schemes possess several advantages over symptom-provoking tests. The subject is relieved of the anxiety of the testing situation and of the distress which a positive reaction engenders. It is true that the guidelines proposed by some practitioners of levodopa loading will reduce the drawbacks:

'We would strongly urge that the levodopa test should not be used in isolated cases for presymptomatic detection, since the potential psychological harm to the individual may far outweigh any possible advantage to him. Investigations should be done only under the guidance of institutions where large samples can be collected and followed, so that the validity of the test can be assessed. (13)

'We would add that a prediction test is useful only for those who have to choose between marriage and celibacy, procreation or interruption of the line of descendants, since no preventive medical treatment can yet be recommended to potential choreic individuals. Bearing this in mind, application of the test to a 50 year old woman seems useless. In young individuals, the test can only be considered after considerable psychiatric work in cases where the individual has shown indisputable proof of his ability to face reality with stoicism. All mass screening programmes, therefore, should be proscribed for this illness. (5)

These recommendations are restrictive in their scope and reflect recognition of the severe ethical

problems inherent in the use of such tests. The statement that 'the patient should only be submitted to the burden of truth that he can carry' (5) indicates the difficult clinical judgements that must be made before their application.

Difficulties are also confronted, however, in the adoption of onset-delaying schemes. Just as provocative tests have been questioned through fear that they might trigger the actual onset of the disease, (14) so there is uncertainty as to whether the symptomatology, severity and duration are altered as a result of delay. Some will liken the procedure to the damming of a river which, on breaching the barrier, issues with greater force than before it was checked. Expressed in other terms, will onset-delay sacrifice quality for quantity of life?

Another drawback, shared by predictive tests, is that the 50 per cent of those at risk who do not bear the gene are needlessly subjected to delaying treatment. Unlike predictive testing, however, the result of such treatment is not shortly apparent, and the more successful the delaying treatment, the longer will be the anxiety generated in the subject. Taken to the extreme, a subject will never know whether he or she carries the gene if treatment is completely successful; this means that any offspring will be ignorant concerning whether or not they are at risk. In the case of levodopa loading, the price paid by a prompt outcome is the ability of the subject to perceive the result of the test.

A further possible problem is unique to onset deferment. In most patients, the appearance of chorea is gradual, insidious and preceded by prodromal symptoms. These may be minor, such as irritability, but occasionally they are major and may give rise to family breakdown, (15) brutality to children, (16) and criminality. (17) These manifestations are controlled when the cause of the behaviour is recognised to be due to Huntington's disease. Onset-delaying plans may cause prodromal symptoms to persist unduly.

A final practical point to be determined concerns the time at which a delaying programme should be initiated. One answer is to derive an estimate of the predicted age at onset of symptoms for the person at risk by means of the interval elapsing between the time of birth and the parental onset age. (18, 19) Such an estimate would provide an upper limit to the age at which the scheme should begin. If this takes the form of pharmacotherapy, tolerance to long-term administration will influence the decision of when to commence.

Duration-extending plans

When the onset of Huntington's disease has finally occurred, the physician is confronted by a situation in which no form of therapy is known to be completely successful. Genetic counselling, in the experience of Whittier, (20) is probably one of the

most potent therapeutic tools, despite its time-consuming nature. Lacking a course of management directed towards the cause of the malady, the neurological signs and psychiatric disturbances receive symptomatic treatment in the hope of bringing them under some measure of control and thus improving the quality of life of the patient. The quantity of life remaining, measured by survival, is much more difficult to control and the progress of disease often depends upon the rate of the dementing process.

The variable presentation of signs and symptoms in the natural history of the disease serves to indicate that schemes to extend survival may be less desirable than those predisposing to a mild course of illness. In practice the distinction may not be important, since severity and duration tend to be inversely correlated and a mild pattern of symptoms is associated with a long period between onset and death. A basic question posed by such considerations is whether the severity, duration and course of the disorder are solely determined by the underlying neuropathology or whether external influences can be brought to bear to promote a more tolerable course of illness. Procedures such as genetic counselling and psychotherapy, aimed at equipping a patient with personal resources to meet the challenge of disease, only become meaningful if the view is held that the predisposing biochemical defect can be modulated by psychological measures.

The factors responsible for a long duration of illness or a mild symptomatology are poorly understood but at present it seems better to concentrate on devising plans to attenuate symptom severity since a long survival period may be achieved at the cost of an intolerable burden of distress to the patient. If such schemes become available, the physician will be faced with the dilemma of whether:

- a) to pursue a conservative policy of allowing the disease to follow its natural course while providing the best possible forms of treatment currently available, or;
- b) to adopt a scheme aimed at increasing the life expectancy of the patient and facing the risk of thereby prolonging severe symptoms by energetic pharmacotherapy, or;
- c) to choose a plan aimed at promoting mild symptoms in the hope that this will not shorten survival or upset the balance between physical and psychological health.

Conclusions

The schemes foreshadowed in this article are in their infancy or, in the case of post-onset plans, largely hypothetical. They are all based on the premise that intervention in the natural history of Huntington's

disease is ethically justifiable and medically desirable. The efficacy of designs to reduce symptom severity or prolong survival can be tested by alternating them with periods of withdrawal. The adoption of pre-onset plans to delay the arrival of symptoms involves decisions whose consequences cannot be foreseen. At best the disorder may be held at bay for a significant length of time at the possible cost of extended prodromal symptoms. At worst the severity of the deferred illness may outweigh the benefit of its delay.

Because onset is irrevocable, it is highly desirable to ease the burden of making such decisions by characterising the type of person, perhaps on the basis of premorbid personality or familial factors, best suited to particular designs for delay. Thus in addition to the need for determining variables significantly predisposing to deferment of symptoms, it is equally requisite to match patient characteristics with the least likelihood of unfavourable consequences.

References

- (1) Goodman R M, Ashkenazi Y E, Adam A, Greenfield G. Thoughts on the early detection of Huntington's chorea. *Advances in neurology* 1973; 1: 273-285.
- (2) Klawans H J Jr, Paulson G W, Ringel S P, Barbeau A. Use of L-dopa in the detection of presymptomatic Huntington's chorea. *New England journal of medicine* 1972; 286: 1332-1334.
- (3) Klawans H L Jr, Paulson G W, Barbeau A. Predictive test for Huntington's chorea. *Lancet* 1970; 2: 1185-1186.
- (4) Cawein M, Turney F. Test for incipient Huntington's chorea. *New England Journal of Medicine* 1971; 284: 504.
- (5) Husquin H, Franck G, Vranckx C. Detection of future cases of Huntington's chorea by the L-dopa load test: experiment with two monozygotic twins. *Advances in neurology* 1973; 1: 301-310.
- (6) Brackenridge C J. Factors affecting the age at onset of Huntington's disease. *Medical journal of Australia* 1980; 1: 261-263.
- (7) Korenyi C, Whittier J R, Conchado D. Stress in Huntington's disease (chorea). *Diseases of the nervous system* 1972; 33: 339-344.
- (8) Brackenridge C J. Effect of climatic temperature on the age of onset of Huntington's chorea. *Journal of neurology, neurosurgery and psychiatry* 1974; 37: 297-301.
- (9) Brackenridge C J. Relation of occupational stress to the age at onset of Huntington's disease. *Acta Neurologica Scandinavica* 1979; 60: 272-276.
- (10) Panse F. Die Erbchorea; eine klinisch-genetische Studie. *Sammlung Psychiatrischer und Neurologischer Einzeldarstellung* 1942; 18: 35-38.
- (11) Spengler M. Verschlimmerung von Chorea Huntington in der Gravidität. *Schweizerische Medizinische Wochenschrift* 1956; 86: 931-932.
- (12) Whittier J R. Research on Huntington's chorea: problems of privilege and confidentiality. *Journal of forensic science* 1963; 8: 568-575.

- (13) Klawans H L Jr, Goodman R M, Paulson G W, Barbeau A. Levodopa in the presymptomatic diagnosis of Huntington's chorea. *Lancet* 1972; 2: 49.
- (14) Cederbaum S. Tests for Huntington's chorea. *New England journal of medicine* 1971; 284: 1045.
- (15) James W E, Mefferd R B, Kimbell I. Early signs of Huntington's chorea. *Diseases of the nervous system* 1969; 30: 556-559.
- (16) Oliver J E, Dewhurst K. Six generations of ill-used children in a Huntington's pedigree. *Post-graduate medical journal* 1969; 45: 757-760.
- (17) Parker N. Observations on Huntington's chorea based on a Queensland survey. *Medical journal of Australia* 1958; 1: 351-359.
- (18) Brackenridge C J, Teltscher B. Estimation of the age at onset of Huntington's disease from factors associated with the affected parent. *Journal of medical genetics* 1975; 12: 64-69.
- (19) Brackenridge C J. Validation and application of an interval factor in estimating the age at onset of Huntington's disease. *Journal of medical genetics* 1978; 15: 23-26.
- (20) Whittier J R. Management of Huntington's chorea: the disease, those affected, and those otherwise involved. *Advances in neurology* 1973; 1: 743-753.