Ethics of a predictive test for Huntington's chorea

S THOMAS

Abstract

"Index Medicus" and 18 other publications have been consulted in an attempt to provide an easily assimilated selection of the recently published and widely dispersed material relevant to the ethical debate the editors of the "BMJ" called for on 4 March 1978. The medical profession is shown to be deeply divided on the ethics of a predictive test for Huntington's chorea. Some members are already using the prospect of a reliable test as an inducement to potential transmitters of this incurable hereditary disease to postpone procreation. Other members would prefer to see any future test withheld from every applicant until such time as radically improved means of treatment or a cure is discovered. The evolution of generally acceptable professional guidelines requires further informed debate.

Introduction

Huntington's chorea is a progressive and incurable disease of the central nervous system transmitted through an autosomal gene with complete penetrance. Each child of an affected person has a 50% chance of inheriting the responsible gene, but carriers cannot be identified until there are clinical signs of the disease itself. By the time these appear, a carrier may well have procreated: roughly two-thirds develop symptoms after the age of 29 years. A predictive test would break new ground by making it possible to identify carriers before they developed the disease. Non-carriers, who now have to wait until late middle or old age before they can be certain that they have not inherited the gene, could learn of their freedom much earlier.

Almost all of the published attempts to develop a definitive test have proceeded on the assumption that the Huntington's chorea gene generates measurable defects long before the clinical features become evident. If this hypothesis is true and the gene does prove to be "switched on" in utero or at any rate early rather than late in the presymptomatic period of a carrier's life, the deliberations of those professional and lay contributors to the ethical debate who are already taking the eventual development of a test for granted will, in retrospect at least, seem timely. Nor could we regard them as entirely wasted if relevant investigations with a different rationale—analysis of the gene's genetic linkage relations, for example—yield all the information that is theoretically obtainable.

At least four features of an ideal test in vivo have been specified in professional publications. Such a test would entail little or no risk to the subject; it would discriminate between carriers and non-carriers with no false positives or false negatives; it would produce no ambiguous results; and its results would be incurable and unchangeable. Although additional features come readily to the minds of individuals at risk, most fantasised additions (prior indication of a given carrier's age at onset, the subsequent survival period, and the nature and severity of symptoms, for example) appear to be contingent on truly prodigious advances in our understanding of the disease's aetiology. For this reason the mainstream of the ethical controversy has been concerned with the impact on the status quo of a definitive but relatively straightforward test.

The status quo

EXTENT OF GENETIC COUNSELLING

At present, only some of the individuals known to be at 50% risk of developing Huntington's chorea are made aware of the medical and genetic implications without delay. A poll in the United Kingdom of choreic families belonging to the Association to Combat Huntington's Chorea, a voluntary lay organisation, showed that whereas couples are quite likely to be cautioned about the dominant inheritance pattern if they have not started a family when the relevant diagnosis is made, couples who already have a young family at the time of diagnosis may not be fully informed until their offspring are old enough to be told. Some family doctors who have seen a generation or more with Huntington's chorea in a given family apparently choose not to tell young women until after they have married and had about two children. Respondents who had produced children in ignorance of the genetic consequences bitterly regretted not being informed at the time and usually regretted having children once they had learnt the

References


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true facts. Nevertheless, 7%, of informed respondents said that they would have preferred not to have been told that their spouse's or relative's disease was hereditary.

**Effect of Genetic Counselling on Those Counselling**

Genetic counsellors have no way of knowing in advance whether someone who is counselled without having actively sought information will be grateful or ungrateful for the risk figures. More important, the 'one-off' 27% that knowledge of these figures is compatible with the mental welfare of everyone counselled. Considering the possible mental anguish and the exceptionally high incidence of suicide in Huntington's families, the dilemma is whether it is humane and ethical to direct a young person's thoughts to the, (at best, or worst), 50-50 chance that he or she might deteriorate into the condition witnessed in a relative, and should govern life accordingly. Thus an individual who might never have consciously or otherwise contemplated the possibility of personal involvement might have life and hope blighted, and survival without development of the disease might be little compensation for a lifetime of anxiety, dread, and single status.

Estimates of the current psychological cost of genetic counselling have to take into account not just the anxiety of those counselled but the anxiety of their relatives and spouses as well.1,2 And national estimates are further complicated by the fact that there is no single lay concept reduced if all individuals counselled. The concept of the disease held by those counselled is likely to be highly specific, shaped by experience of it in a parent or other relative. The hypothetical daughter of case A, a Northamptonshire case-history, is unlikely to think of Huntington's chorea in exactly the same way as the hypothetical daughter of case B. Case A:1 'Age of onset 54, with excessive tiredness, difficulty in walking, nervousness, insomnia, and hypochondriasis. Choreic movements and personality changes ensued, followed by progressive dementia. He died aged 64.'3 Case B:4 'Age of onset 43. Earliest features included restlessness, headache, insomnia, violence, irritability, loss of work, and thinning. This resulted in his wife leaving him, his child being brought up by the grandparents. Subsequently he developed mild-to-moderate choreathetotic movements and severe ataxia. Dementia progressed rapidly from the age of 35.'5,6

To be strictly accurate, calculation of the total posterior probability of someone who has a parent with Huntington's chorea being symptomless at a given age and not having the gene must be based on a knowledge of the ranges of ages at onset of Huntington's chorea in that region.7 As age at onset has been regarded as a very vague retrospective point which is notoriously difficult to assess,8 and there is in any case a shortage of regional studies that purport to be comprehensive, those who when counselled simply-mindedly prefer to accept the prodromal probability figure of 50%, risk in all symptom-free periods of their lives raise ticklish problems. Given the nature of the relevant statistical evidence and the availability of at least one series of curves that attempts to take into account the ranges of parental ages at onset and their modifying effect on the actual risk, what revised figures, if any, should such people be urged to accept?

Experience has shown that 'The ambiguous condition of 50% risk is extremely difficult to maintain in one's mind, if not impossible. In practice a 50-50 risk translates to a 100% certainty that one will or will not develop the disease, but the certainty changes from one to the other from moment to moment, day to day, month to month.'9 Although such vacillation can make a whole range of personally important decisions difficult to take, studies of the disease have naturally concentrated on the striking implications of the choice between procreation and interruption of the line of descent.

**Effect of Genetic Counselling on Reproduction Rate of Those Counselling**

Huntington's chorea is still quite rare (7.6 per 100,000 population in South Wales8 and usually 2-7 per 100,000 elsewhere,10 and the proportion of cases that represent fresh mutations is extremely low (1-2% in South Wales11 and probably not much more than 5%, elsewhere.12 Theoretically, the mean number of generations each mutant gene survives, and hence the prevalence of the disease,13 could be substantially reduced if all individuals at risk were counselled and either had no children or reproduced at less than replacement rate. In practice, the variable, insidious, and usually late onset of Huntington's chorea, coupled with professional determination not to burden families with a misdiagnosis and concern for the peace of mind of definitively diagnosed patients and their families, have proved formidable obstacles to a comprehensive early-warning system.

In South Wales, where a co-ordinated programme of counselling and family support is under way,14 66% of an original sample of 92 patients with Huntington's chorea in South Wales were found to have "worthwhile" genetic information before completing their families. Of a total of 77 high-risk adults who were counselled early, 52 said that they intended to have fewer children as a result; but the other 25 denied being influenced in this way.

Some offspring of affected parents evidently feel that a deliberate interruption of the line of descent is tantamount to an admission that they themselves will develop the disease. An American woman who had a tubal ligation rather than risk passing on the Huntington's chorea gene felt she was damned if she did and damned if she didn't. 'If she tried to accept the fact that she might accept the fact that she might have Huntington's disease: if she thought she might remain healthy, she could not bear the thought that she had had herself sterilised for no reason. It was extremely hard for her to act in one circumstance as if she would have Huntington's disease and take appropriate precautions and still maintain the belief that she could as likely be well.'15

As much as a decade can pass between the start of prodromal symptoms and the first tentative diagnosis,16 and possibly the distress and incertitude that the family and the person involved face in the first stages of their illness make some of them incapable of using effective measures of birth control. On this view, as on the view that the urge and determination to procreate in the face of the possibility of the disease is almost a prodromal symptom of the disease itself,17 any reduction in family size as a result of genetic counselling is likely to come preferentially from those who do not have the mutant gene. The programme in South Wales will allow these pessimistic hypotheses to be tested, but not, unfortunately, for some years yet.

**Predictive Testing**

**Extent of Lay Demand**

Questionnaires that gave respondents no reason to suppose that radically improved treatment or a cure would become available in the immediate future produced the following results. In the United Kingdom 80% of respondents from families with Huntington's chorea said that they would like family members to be tested if a 100% reliable test existed; in the United States 77% of respondents at 50%, risk reported that they were willing to be tested.18 In the Australian State of Victoria, where subjects were selected from disease pedigree files (unlike their British and American counterparts, who were drawn from voluntary lay organisations), 84% of respondents at 50% risk had a positive attitude towards a safe, simple, and 100% certain test, and 64% had a generally positive attitude towards predictive testing.19

**Effect on Those Tested**

The potential benefits for about half of the counselled offspring of patients with Huntington's chorea are not in dispute: "the person who does not have the gene will be reassured that the disease will not develop and, resulting from this, he will be told that he can have children, safe in the knowledge that they will also be unaffected."20

The price of the non-carrier's peace of mind would be the carrier's certainty that he or she would develop the disease and might transmit it. For if a tester equivocated about a positive result, and allowed a carrier to procreate in the belief that he or she might not have the gene, there would be justifiable resentment when the symptoms inevitably appeared; and an opportunity to try to reduce the incidence of the disease by early disclosure of the unfortunate facts would be lost. In practice it would be impossible to deceive all carriers by equivocation because many would compare notes with tested non-carrier siblings, and when they learnt that the latter had been given the freedom to have children the realisation that they themselves had the gene would not be far away.21

It has been said that carriers will be "plunged into despondency when they learn that their fate is to be the gradual physical and intellectual decline that the disease inevitably brings . . . depression and the risk of suicide would be more or less inevitable."22 This crucial prediction has been challenged by at least one practitioner23 and by a lay contributor to the debate. According to the lay contributor: "There is understandable reluctance on the part of the medical profession to tell a patient that he or she is destined to acquire an
incurable disease. The argument seems to be that, since nothing can be done, such news deprives the patient of hope and thus increases the risk of severe depression and suicide. There are two flaws in this reasoning. The first is that because Huntington's disease is more treatable than ever before, because of the existence of such organisations as the Committee to Combat Huntington's Disease, and because many patients with Huntington's disease live happy, useful lives for many years after the onset of symptoms, there is more reason than ever before for families with Huntington's disease to have hope. Secondly, although extremely early diagnosis serves no medical purpose, it can give a person time to prepare emotionally, financially, and in other ways, so that when the symptoms appear they are not so devastating to the patient and family as they might otherwise be. Giving the patient time to cope, prepare, and plan while still healthy may actually reduce the possibility of suicide."

Identified and informed carriers might well want to reproduce at a lower rate, overall, than individuals who believe themselves to be at 50% risk. Analysis of the carefully and conscientiously made declarations of intent in the British study already referred to lends some support to this view. More specific predictions are likely to be found if, as has been suggested, "the human drive for procreation springs from a well so deep that it will always override and take control of human intellect, blending all reason and argument into rationalisation through the process of projection and denial."22

Discussion

Given the absence of a uniform lay concept of Huntington's chorea, the range of personality types likely to be found in a group as large as the "pro-test" population appears to be, and the conflicting forecasts of the psychological implications for tested carriers, a useful starting point for future discussion of the pros and cons of pre-cure testing (in the absence of a cure for the disease) might be to acknowledge that we have no way of knowing whether most tested carriers would react constructively or destructively.

For several reasons, the experiences of the 28th or so documented subjects of an experimental levodopa-based predictive test must not be regarded as directly applicable to other tests. Levodopa itself can cause depression with concomitant suicidal tendencies46 and a positive result, while distressingly producing the phenotypic expression of the disease,7 falls short of proving Huntington's chorea (at this stage, as subjects are presumably told, it merely increases the prediction coefficient16 47). Useful analogies with the experiences of diagnosed victims of progressive disorders other than Huntington's chorea have been suggested,15 but these too leave unclear the impact of a definitive predictive test for Huntington's chorea that is not based on levodopa.

If a reliable test were to be devised before the discovery of a cure, one thing at least seems plain. To turn away every applicant for testing in a well-intentioned and advocated68 endeavour to safeguard the presumed best interests of carriers would be an extremely controversial course, both within the profession33 and outside. For even when the results of the two polls derived from voluntary lay organisations are discounted to some extent, as a sensible precaution against notional sample bias, the high and broadly comparable levels of support for predictive testing in all three polls show that many of those counselled believe that early certainty about the gene would be easier to bear than the present protracted uncertainty.

Until such time, if any, as this belief is shown to be completely groundless, no application for a test should be dismissed out of hand. Each application should be considered on its particular merits. And to reject the applications of couples who have followed medical advice to postpone procreation for five years49 in the fostered expectation that screening will immediately follow the invention of a reliable test should surely be a last resort.

I wish to thank Sir Martin Roth for a most helpful discussion of some aspects of predictive testing. My interest in the subject, which was stimulated by the occurrence of the disease in a relative, is a layman's interest. Unattributed opinions in the article, though rarely wholly original, are personal in the sense that they cannot responsibly be laid at the doors of named individuals or organisations. The Association to Combat Huntington's Chorea, to which I belong, has no official policy.

Readers who wish to make good the deficiencies of so brief a survey will find further references relating to the feasibility and desirability of predictive tests in vivo (and in utero) in M R Hayden's Huntington's Chorea,3 which provides an overview of the state of current knowledge concerning most aspects of the disease. Additional information about the status quo in the United Kingdom may be obtained from the National Office of the Association to Combat Huntington's Chorea, Borough House, 34a Station Road, Hinckley, Leicestershire LE10 1AP.

References


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