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Prenatal testing for Huntington's disease: experience within the UK 1994-1998

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Huntington's disease (HD) is an adult onset, autosomal dominant disorder[1] with onset of symptoms usually in the fourth or fifth decade. The classical triad of clinical features, movement disorder, cognitive impairment, and personality and psychiatric disorder, cause serious management problems. There is significant morbidity within the affected families, especially for those who themselves are at risk of developing the disease. HD affects about 5000 people in the UK and about five times that number are considered to be at 50% risk of developing the disease.

Since the mapping of the locus for Huntington's disease on chromosome 4 in 1983,[2] followed by the identification of the gene and its expanded polyglutamine repeat in HD in 1993,[3] it has been possible to offer accurate tests for HD. Prenatal tests and presymptomatic predictive tests for adults at risk for HD are available at genetic centres throughout the world.

There are two common approaches to prenatal testing in HD. Direct testing involves investigating for the presence of the mutation in a pregnancy. This gives an accurate result. If the status of the at risk parent has not been ascertained, then this may produce predictive information about that person.

In exclusion testing, the at risk grandparental chromosome 4 locus is excluded using linkage analysis. This test preserves the 50% risk of the parent, and allows a pregnancy at low risk to continue. In this situation, pregnancies that share the risk of the parent would be terminated. However, should the at risk parent not develop HD, a normal pregnancy would have been lost.

Given the technical feasibility of prenatal mutation testing and the severity of the disorder, it might be expected that prenatal diagnosis would be frequently requested.

Tyler *et al*[4] reviewed a group of referrals for exclusion testing in pregnancy, and surveyed a group of subjects at 50% risk of developing HD about their attitudes to prenatal testing. They concluded that the demand for such testing was likely to be small. We considered it important to assess this demand in relation to that for presymptomatic testing, and since the numbers recorded by individual centres were small, to collect the data on a UK basis.

In Britain, the UK Huntington's Disease Prediction Consortium was created to monitor the use of molecular testing in HD, to evaluate the developing service, and to ensure the highest standards were applied to the procedure.[5] Several studies before the introduction of predictive testing reported the views of those at risk of HD. These showed that between 56% and 80% of at risk subjects would undergo predictive testing once it was available.[6–8] Uptake of such testing has been considerably less than this, 9-15%[1] with some exceptions.[9]

Table 1 Prenatal tests and their outcome (UK) 1994–1998

	1994	*1995*	*1996*	*1997*	*1998*	*Total*
Exclusion tests						
Outcome: low risk	13	4	3	8	6	34
Outcome: high risk	7	5	8	9	6	35
Outcome: uninformative	3	0	0	0	0	3
Terminations	7	5	8	8	6	34
Miscarriage	0	0	0	0	1	1
Total	23	9	11	17	12	72
Direct tests						
Outcome: low risk	8	4	12	10	12	46
Outcome: high risk	6	2	1	8	11	28
Terminations	6	2	1	5	11	25
Total	14	6	13	18	23	74
Total (all tests)	37	15	24	35	35	146

The consortium has recorded all presymptomatic predictive tests since testing began in 1988, a total of 2937 up to the end of December 1997. Less than 50% of these have been unfavourable results. Data on all prenatal tests recorded in the period 1994 to 1998 form the basis for the study reported here. Anonymised data on each test performed in pregnancy were collected on an annual basis from each of the member centres of the United Kingdom Huntington's Disease Prediction Consortium. Information on referrals during pregnancy that did not lead to testing did not form part of this study.

One hundred and forty six prenatal tests were recorded in the years 1994 to 1998 (table 1). This includes one twin pregnancy.

Forty five percent of tests (65) occurred where the parent was aware that they had the mutation for HD. Nine of these parents were described as having clinical features of the disease at the time of the pregnancy.

Fifty four percent of tests (78) were carried out in pregnancies where the parent was at 50% risk. Eight of these were accomplished using mutation detection, that is, the at risk parent was prepared to find out that they too had the mutation as a result of investigation of the pregnancy. In three cases, presymptomatic predictive testing was performed during the pregnancy and before the pregnancy was investigated.

In two cases, the parent was at 25% risk, that is, the grandparent was asymptomatic but at 50% prior risk.

Sixty six (43%) unfavourable results have been produced, but only 61 terminations performed. In one of the four cases where the pregnancy continues, the pregnancy shares the parent's 50% risk as the result was produced using exclusion testing. In the remaining three cases, the mutation was detected in the fetus.

There was one report of miscarriage as a result of the prenatal investigation, in a twin pregnancy.

The decision to investigate a pregnancy for an adult onset disease (and possibly terminate that pregnancy) is never an easy one, and lately the families have expressed much hope that a cure will be found for the disease and therefore they would be able to avoid termination of a pregnancy. HD can be variable in severity, and undoubtedly experience of later onset disease, which may be less severe, can encourage couples not to investigate their pregnancies.

Many people who present for predictive testing already have at least one child.[10] The trend is for these subjects not to test pregnancies that occur after they have received an unfavourable result, since they would then have children at 50% risk and children whose status was certain.

The trauma associated with termination of any pregnancy is considerable. Tolmie *et al*[11] described a group of UK families (an earlier group who are not included in this study) who had difficulty with their decision to terminate an at risk pregnancy following exclusion testing. Three of nine high risk pregnancies were continued. Clarke *et al*[12] showed the problems of producing predictive information for an adult onset incurable disease. In cases where an unfavourable result is produced, but the pregnancy continues, these children will grow up with certainty of information about their status, having had no choice in the decision. In addition, their parents are aware of their status, and their prejudices and those of society will undoubtedly be disadvantageous for them. There are only four such cases in this series.

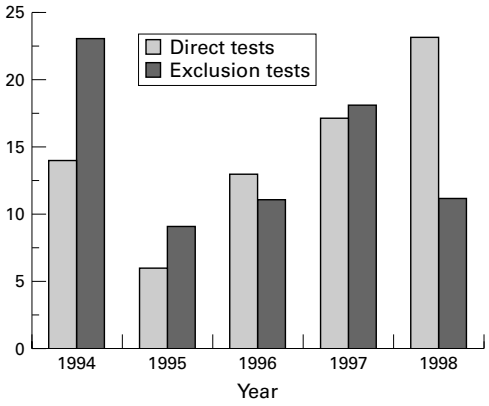

Figure 1 Direct testing and mutation testing 1994-1998.

There are couples who have undergone tests on as many as five pregnancies in their efforts to ensure that no child of theirs would have to suffer the problems of being at risk as they had themselves (S Simpson, personal communication).

Many couples express their anxiety about any child of theirs growing up with an affected parent, even if it were known that the child would not be at risk because of prenatal testing. These people may have grown up in a family where alcoholism, suicide, and divorce are common.[13] Those who have had an unfavourable result by predictive testing and then have chosen to have a pregnancy are in the minority in this group.

Other options are available to those who know they have the mutation and who wish to have children. In at least one case, after the termination of a high risk pregnancy, the couple chose artificial insemination by donor. However, couples who have attempted to adopt or foster have had considerable difficulties because of the at risk status of one of the partners.[14 15]

It is now becoming possible to offer preimplantation diagnosis[16 17] to couples who do not wish investigation of an established pregnancy. This technique remains at a research stage; only preliminary data are available for its use and the rate of successful implantation of the fetus remains low. Nevertheless some patients in the clinic setting have expressed interest, but accurate figures are not available.

For those at risk who decide not to undergo presymptomatic predictive testing, the opportunity to ensure that the gene is not transmitted to the next generation remains with the use of exclusion testing. For some subjects their commitment is absolute (see above) and they have repeated attempts to have a pregnancy with a

low risk. Forty nine percent of the total tests in this series were performed using exclusion testing, although there has been an increasing number of tests using direct mutation testing in the last three years (fig 1). These data provide evidence that many at risk subjects would prefer not to know whether or not they are going to develop HD, but such is their experience of the disease and their at risk status that they wish to prevent the birth of an at risk child.

Maat-Kievit *et al*[18] described the experience in The Netherlands of 72 prenatal tests in Huntington's disease. As in our study, a trend towards an increasing number of direct tests has been observed, although exclusion testing is still seen as a useful tool for those who do not wish predictive testing.

In a survey of subjects from Germany[19] who were at risk of HD, over 67% indicated that they would wish to undergo presymptomatic predictive testing themselves, but only 45% would wish to use prenatal diagnosis. Twenty seven percent of those questioned stated they could not use prenatal diagnosis because they felt they could not terminate a pregnancy.

In South Africa, 59 subjects who had undergone predictive, diagnostic, or prenatal testing for HD were reported.[20] The two affected pregnancies were aborted, from a group of 10 who had undergone prenatal tests.

In a review of international data, Evers-Kiebooms *et al*[21] showed that more prenatal tests took place where the male was at risk. This may indicate that the female role of child care was recognised by the families, in that if the male were subsequently affected, child care would continue.

Only a minority of those at risk of Huntington's disease in the UK have chosen to prevent the transmission of the disease by the use of prenatal diagnosis. There may be lack of knowledge among the at risk population about the tests available[22] and older family members and spouses occasionally deliberately withhold information about the presence of the disease within the families. This may also help to explain the low uptake of presymptomatic predictive testing in the UK, but it does not explain why the number of those requesting prenatal diagnosis is so small in comparison with the number of requests for predictive testing.

The families in general express great hope for the future[22] for treatment or prevention of HD and the low uptake of prenatal testing may reflect this. The continued use of exclusion testing in pregnancies, despite the ready availability of accurate direct testing, also shows the usefulness of exclusion testing for those who do not wish to obtain accurate information about their own status, but who are unwilling to risk transmission of the disease.

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