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Opinion: Predictive Testing for Huntington Disease in Childhood: Challenges and Implications

M. Bloch and M. R. Hayden

Department of Medical Genetics, University of British Columbia, Vancouver

Introduction

Most diseases for which predictive testing or DNA analysis is now possible are early-onset diseases such as cystic fibrosis, Duchenne muscular dystrophy, and Tay Sachs disease. Prenatal testing in this situation can be used to detect high-risk pregnancies, so that parents have the option of either ending the pregnancy or continuing to term. Should parents decide to continue such a pregnancy, the affected child would develop the disease early in life. This situation is very different for Huntington disease (HD), an adult-onset genetic disorder.

HD is a neurodegenerative disorder, characterized by involuntary choreiform movements, personality change, and cognitive decline. Onset is most common in the third and fourth decades of life, with inexorable progression to death 15–25 years after onset. The biochemical defect underlying HD is not known, and there is no treatment to halt progression of the illness (Hayden 1981).

The discovery of numerous polymorphic DNA markers linked to the mutant gene has made predictive testing for HD possible (Gusella et al. 1983; Hayden et al. 1988; Meissen et al. 1988; Wasmuth et al. 1988; Brandt et al. 1989). HD, which has a profound effect on the lives of persons at risk, is especially suitable for predictive testing. The inheritance is clearly autosomal dominant, with no demonstrated genetic heterogeneity (Conneally et al. 1989), and the clinical course is well recognized. In contrast to the more usual DNA analyses, persons at risk for HD may learn about the possibility that they will develop a devastating disease sometime in the future. They will also learn that there is no treatment which can modify this outcome. Such testing is fundamentally different from assessment of risk for other dominant genetic disorders, such as familial hypercholesterolemia, where individuals at high risk may, with diet or drugs, modify the course of the illness.

Predictive testing for HD will serve as an important model for delivery of such a test for other late-onset incurable genetic disorders, and the guidelines developed in the former may be directly applicable to such programs. Programs for predictive testing for HD are currently underway in Europe and the United States. A national program for this purpose has been established in Canada. The protocols for predictive testing in Canada were developed with the support of an advisory board including local ethicists, other professionals, and members of the HD Society of Canada (Fox et al. 1988) and in discussion with the other major predictive testing programs, in Boston (Meissen et al. 1988) and Baltimore (Brandt et al. 1989).

A primary principle in the establishment of these predictive testing programs was the decision to offer the test only to persons above the age of 18 years. The intention in doing this was to ensure that the person participating in predictive testing was acting autonomously with a full understanding of the benefits and risks of predictive testing.

Recently we have received requests to test minor children. This editorial is an opportunity to state the reasons why we do not feel this is appropriate and to discuss some of the implications arising from this policy.

Should Children be Tested?

A number of parents have requested predictive testing for their minor children. Their reasons have usually been expressed in terms of the best interests of both the child and the family. These reasons have included gaining knowledge which will reduce the uncertainty with which the children must live and which will facilitate rational planning for the future of the child and for the family. Some parents have requested that their

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Address for correspondence and reprints: Dr. Michael R. Hayden, Department of Medical Genetics, F168 University Hospital, 2211 Wesbrook Mall, Vancouver, British Columbia, V6T 2B5, Canada.

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children be given the test because they are curious about their children's status and wish to allay their own anxieties.

One of the major ethical principles which guided the development of our program has been the principle of autonomy. The principle implies an inherent respect for a person's right to decide what is best for him- or herself. As in other genetic counseling situations, there is also an obligation on the part of the counselor to support that decision.

Numerous important guidelines for predictive testing derive from this. Genetic counselors must aim to provide the most accurate information to the participants in predictive testing, so that they are fully informed and are not unduly influenced by other persons or institutions. Children clearly cannot make an informed decision about whether to participate in predictive testing. The request is made by a third party, in this instance a parent. The only justification for doing predictive testing in childhood is if an advantage can clearly be demonstrated for the child. There is currently no known treatment which might prevent or delay the age of onset for HD. Such testing may be disadvantageous for the child, either because of possible distortion of parent/child or sib/sib relationships or because of limitation of resources for the child shown to be at increased risk. The self-esteem and sense of worth of a developing child may be profoundly and negatively affected. The attitude of society and its agencies toward high-risk individuals has not yet been clarified. Since no treatment is available and there is the possibility of harm, we oppose the testing of children.

DNA Testing for a Child with Symptoms: Risk Modification—Not Diagnosis of Disease

Parents who have a child at risk who presents with some neurological or behavioral change have requested predictive testing so that they might know whether this change represents HD. This difficult situation may arise when a child at risk for HD manifests some changes which, in the minds of the parents, heralds the onset of the disease.

This may arise in two different situations; first, the parent may be found to be either at an increased risk or affected with HD, and consequently the child is at 50% risk; second, the parent may be at 50% risk and the child may be at 25% risk but now manifesting some behavioral or neurological changes. The latter situation has occurred previously on rare occasions when the child at 25% risk develops signs of HD before manifestation of HD appear in the parent.

If DNA testing were performed in either of these situations, this would only result in a probability statement about whether the child had inherited the HD gene. It would provide no information whatsoever as to whether the symptoms that the child has at this particular time are due to HD. DNA testing does not provide *any* information about onset of HD. The danger of using predictive testing for diagnosis of disease is that symptoms which are not due to HD may be wrongfully attributed to the early manifestations of the disorder. Furthermore, even if an increased risk is demonstrated for the child, the crucial question of whether the child's present symptoms are due to HD remains unanswered. This can only be decided by a detailed clinical examination.

The diagnosis of HD in childhood is often missed in the earliest phases, and this does cause considerable distress to the parents. However, a careful family history, together with detailed assessment of neurological changes and a CT scan, and a careful follow-up may allow a neurologist to make the diagnosis of HD. Furthermore, even if DNA testing were to suggest that the child had not inherited the gene, the finding of unequivocal signs of HD on neurological exam would outweigh the linkage analysis.

We recently received a request from parents to test a child for HD who has had mild irritability and general behavior problems which have been intermittent for a period of 3–4 years. These are common and nonspecific findings in childhood, and this presentation is unlikely to herald the onset of HD. In this situation a DNA result which raised this child's likelihood of having HD could be misinterpreted as confirmation of the diagnosis. Yet, this child is unlikely to have signs of HD, and thus this procedure would constitute predictive testing of a minor, with all its potential problems. Given the difficulty in interpreting a DNA result in the face of dubious signs of HD and the fact that it is unnecessary when signs are obvious, DNA tests to support a diagnosis of HD in adulthood or childhood should not, in our judgment, be undertaken.

Request for Testing Related to Adoption

Adoption agencies have requested testing of a baby in order to facilitate placement for the child. Adoptive parents have an established right to know the risk that their adoptive child may have inherited a genetic dis-

ease. However, we concur with Morris et al. (1988) that predictive testing could have negative effects on the child's upbringing and education, if the child had a significantly increased risk. Furthermore, the differential impact on two siblings with different test results may result in separation of siblings, with consequent harm to both.

In a different situation an at-risk parent may request testing of an infant or fetus so that a decision about adoption could be facilitated. Recently a 25-wk-pregnant woman, who was at 50% risk for HD, requested prenatal testing. She had decided that if the test showed a low risk she would keep the child, whereas if it showed an increased risk she would give the child up for adoption. This request was not raised by the adoption agency but by the single parent, who did not wish to raise a child at increased risk for developing HD. In this situation, as in the case of requests from an adopting agency, testing would not be performed, because such testing would not be in the best interests of the child.

Impact on Prenatal Testing

The principles of best interest of the child and autonomy have a major impact on the practice of prenatal testing for HD. Prenatal testing for this late-onset disease is complex and demanding because of the different options available (Fahy et al. 1989), the varying motives of the parents, and the frequent acute and pressing circumstances under which it occurs. Prenatal testing can be undertaken when a parent is affected or has an increased risk for HD and when the fetus has about a 50% a priori risk of having inherited the HD gene. A different situation occurs when the parent is at 50% risk for HD and when the fetus has an a priori risk of 25%. In this situation the prenatal testing will result in a fetus which has either a very low risk of inheriting HD or a risk similar to that of the at-risk parent; this is so-called exclusion testing (Quarrell et al. 1987). In addition, if this at-risk parent ever develops HD, then in all likelihood the child will also develop HD.

The usual principles of genetic practice would entail offering prenatal testing for a genetic disease but would not suggest any directive counseling with regard to the parents' choice for the outcome of that pregnancy. These principles for prenatal testing are primarily directed toward assessment of childhood-onset diseases. However, there is no obivous appropriate precedent for DNA evaluation for this late-onset incurable disease. Principles of practice derived from previous situations in which DNA analysis has been applied should not immediately be extrapolated to this situation. In order to protect the interests of the child, we have had to explore with parents the likely outcomes for the pregnancy. If the parents do not plan to terminate the pregnancy in the event that the risk to the fetus is increased, this would result in the birth of a child with a known increased risk for HD who may be subjected to all the dangers and problems described previously.

The dilemma in this situation is that parents who do not see termintion of pregnancy as an option will not have the opportunity of obtaining information that their continuing pregnancy is at low risk for having inherited the gene for HD. The situation becomes even more complex for exclusion testing in which the most difficult outcome is that the fetus has a risk similar to that of the at-risk parent, a risk which would be in the order of 50%. Counseling aims both to explore with the parents the possible choices that they would make with regard to the outcome of the pregnancy and to inform the parents of the dilemmas of learning about the status of their children in their particular circumstances. We have found that some parents have withdrawn their requests for prenatal testing in this situation. These dilemmas in prenatal testing necessitate the need for the availability of in-depth counseling to help parents with this difficult decision.

In view of the fact that we are currently involved in a research program to develop guidelines for HD, we are offering both definitive and exclusion-type prenatal testing. We have found that parents either at risk for or affected by HD are unlikely to proceed with prenatal diagnosis if, with regard to the pregnancy, they do not plan to make any decision based on the outcome of prenatal testing. Parents have understood that this would be similar to testing a minor child and in general have understood the significant implications of such a choice.

In our program eight exclusion prenatal tests have been done, with five resulting in an increased risk for the fetus. In four instances the parents decided to terminate the pregnancy, and in the fifth instance the parents reconsidered their situation and have now decided to continue the pregnancy, which will result in the birth of a child at increased risk for HD. The future impact such information will have on this child and on the child's relationship with the parents is unknown. While this situation cannot always be prevented, the likelihood of this occurring can be diminished by providing appropriate counseling in relation to prenatal and exclusion testing.

Summary

Predictive testing for HD strongly highlights the need for autonomy and the need for each individual to decide about his or her willingness—or unwillingness—to obtain genetic information predictive of the future outcome. In respect of this principle, testing for minors should not be offered at the request of a third party, and prenatal testing which would result in the birth of a child at increased risk for HD should, where possible, be avoided. If we accede to the wishes of the parents for their children to be tested, we will have broken the primary principles of confidentiality, privacy, and individual justice that are owed to those children. This could be the thin edge of a wedge which could result in adoption agencies, educational institutions, insurance companies, and other third parties demanding genetic testing for another individual.

Despite years of careful planning, predictive testing for HD is turning out to be more complex and challenging than ever expected. We need a great deal of care and concern in developing our response to this challenge. Careful long-term assessment and documentation of the impact of such testing is needed, so that the appropriate guidelines can be developed, guidelines which both protect families with HD and at the same time give individuals the opportunity to participate in predictive testing programs.

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