FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.13, No 2, 2006, pp. 74 - 77 UC 616.851:616-079(497.2)

THE IMPLICATION OF THE FIRST PRENATAL DIAGNOSIS FOR HUNTINGTON DISEASE IN BULGARIA AFTER PREDICTIVE TESTING

Ivanka I. Dimova[1], Stefan Wieczorek[2], Violeta G. Dimitrova[3], Albena Krasteva[4], Stoyan G. Lalchev[1], Draga I. Toncheva[1]

[1]*Department of medical genetics, Medical University, Sofia, Bulgaria*
[2]*Ruhr–University Bochum, Human Genetics, Germany*
[3]*Fetal Medicine Department, University Hospital of Obstetrics and Gynaecology "Maichin dom", Sofia, Bulgaria*
[4]*Clinical Psychology, University Hospital of Paediatrics, Sofia, Bulgaria*
E-mail: dragatoncheva@yahoo.com

Summary. *The issue of carrier testing for Huntington's disease (HD) gene is controversial. Careful counselling and follow-up is needed if asymptomatic family members at risk are tested. Though test results are "black or white" in >99% of cases, their interpretation may be quite problematic and difficult in individual cases. Although the identification of the HD gene mutation has facilitated predictive testing, there is no treatment available to slow down or alter the disease progression. Therefore, carrier testing is associated with numerous emotional, practical and ethical concerns. Appropriate genetic counselling and support is necessary in such cases. We present our experience in predictive testing of HD, underpinning essential steps of the testing procedure: evaluation of the motives, psychological assessment before and after the tests and consistent support of the patient/couple during the entire process as well as of their subsequent reproductive decisions.*

Key words: *Huntington disease, predictive testing, repeat expansion mutation, genetic counselling*

Introduction

Huntington's disease (HD), called also Huntington chorea, is a severe neurodegenerative disease with autosomal dominant pattern of inheritance. HD was first described by George Huntington in 1872. Its incidence is 5-10/100,000 (1). It is caused by a mutation of a single gene on chromosome 4. The mutational mechanism comprises pathogenetic expansion of a polymorphic microsatellite (CAG)n within the coding 5' region of the gene (2). The number of CAG repeats ranges from 10 to 35 copies in normal chromosomes, while on HD chromosomes the number of repeats is from 36 to more than 200 (3). Measurement of the (CAG)n block length in the HD gene provides direct diagnosis of HD. Statistically, the greater the number of repeats, the more likely is that the person will develop symptoms at younger age. Every child of a parent with the disorder has a 50% chance of inheriting the mutant allele and developing HD. The disease onset may occur earlier and the clinical manifestation may be more severe in each succeeding affected generation because the number of repeats can increase, especially during paternal transmission - a phenomenon, called anticipation (4).

The main clinical manifestation of HD is chorea - the Greek word for "dance," used to describe involuntary movements of the body affecting especially the arms, the legs and the face (5). In Huntington's chorea, these movements tend to be spastic and ballistic and they dramatically affect normal daily activity. They are due to slow neurodegeneration involving predominantly the basal ganglia. The symptoms of the disease are caused by a significant reduction of two principal neurotransmitters (naturally occurring chemicals in the brain) - namely acetylcholine and GABA. This in turn affects the activity of the neurotransmitter Dopamine, which is increased (6). The disease progresses and leads to dementia and slowed eye movements. Most commonly, the onset of the first symptoms is around 40-50 years of age. The degeneration slowly progresses ending with lethal outcome some 10 to 20 years later (7,8), mainly due to consequences of bedriddenness and cachexia.

In future, causal treatment of HD including gene therapy may become available. Until successful introduction of such strategies, the only effective approach is prevention, based on genetic counselling (9). Genetic counseling is indicated, depending on the free will of those concerned, whenever there is a family history of HD. This may include pre-test counselling (before delivery of test results), counselling regarding the opportunities for prenatal diagnosis and counselling regarding reproductive choices. DNA testing may be performed in one or several family members – asymptomatic or symptomatic. Since the odds for the child of a person with HD to be affected are considerably high (50%), individuals carrying the mutation may wish to consider

adoption or forms of assisted reproduction (oocyte donation, heteroinsemination) that reduce the risk of the disease to be passed on to their children.

During pre-test counselling individuals are provided with all necessary information regarding HD and its various symptoms, details on how predictive genetic testing is conducted, and information regarding additional diagnostic screening procedures. A particular problem is that the (CAG)n block length of the HD gene does not provide accurate information concerning the approximate age at onset, clinical severity or rate of disease progression (10-12).

So far, there was no experience of pre-symptomatic testing for HD in Bulgaria. Testing is associated with numerous personal and ethical issues, since the disease has late onset and a more or less predictable clinical course. Here we present our approach with the pre-symptomatic testing for HD of an asymptomatic 22 years old man with family history of the disease (Fig. 1). He lived long time with the question of his mutation carrier status. He was just married, and the couple considered future pregnancies. Since his test result was positive for HD it was followed by prenatal testing of the fetus after his wife became pregnant.

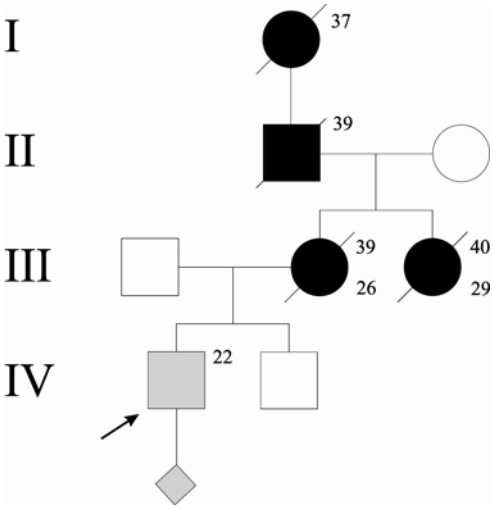

Fig. 1. Pedigree of the propositus
Legend: arrow – pre-symptomatic mutation carrier who visited genetic counseling service; black symbol – HD affected individual; grey symbol – non-symptomatic mutation carrier; strike-through symbols – dead from HD; upper number – the age of the death or at the current moment; lower number – the age at onset of HD.

We paid special attention to the psychological assessment, with an approach being built on motivation-based genetic counseling. The primary motif for predictive testing of our patient was the assessment of the risk for transmission of HD to his offspring. Moreover, he was highly motivated to restrict disease transmission in his family because of the severe clinical manifestation in his affected relatives. Further, his wife was highly motivated to have prenatal diagnosis during her pregnancy.

Methods

Psychological assessment

The propositus was referred for psychological assessment before and after DNA testing. Assessment of depression and anxiety was performed by the test of Zung (13) and the test of Taylor (14, 15), respectively. Questions in the Zung test have four scales of answers with different rating: scale 4 – 1 point, scale 3 – 2 points, scale 2 – 3 points and scale 1 – 4 points. The evaluation of the depression is based on score as follows: < 50 points – normal range; 48-59 points – mild depression; 60-69 points – sub-depression; > 70 points – real depression. The test of Taylor consists of 47 questions with answering alternatives (yes/no). The anxiety is evaluated as follows: 0 -17 points – normal range; 18-28 points – increased anxiety; 29-32 points – neurosis; 33-50 points – reactive depressive state.

DNA testing

Informed consent was requested from participant prior to genetic testing. The DNA from peripheral blood was extracted according to a standard phenol-chloroform protocol. The disease causing part of the HD gene was amplified by radioactively labeled PCR and the products were analyzed on denaturating polyacrylamide gels at the Ruhr-University of Bochum/Germany.

Results

DNA testing revealed that the propositus was HD mutation carrier with 18 (±2) CAGs on the normal allele and 51(±2) CAGs on the expanded allele. The genetic service supported him before testing, in relation of disclosing the test results and after that. It also carried out psychological interviews. Genetic counseling was offered to and accepted by the patient's wife who helped him with great empathy to cope with the results.

Anxiety before testing was in the normal range (13 points) and remained the same after testing (6 points), which was beneficial for the acceptance of the results. Depression decreased from real (73 points) to sub-depression (68 points), probably due to the support of his wife in the context of competent genetic counseling. During three consecutive sessions the patient was gradually adapted to receive the result from the DNA analysis. The result was presented to the patient when the rate of real depression had decreased to sub-depression.

A year later the wife of the patient became pregnant. Because of the high risk for transmission of the mutation to the fetus, chorionic villus sampling (CVS) was performed in the 11th week of gestation after informed consent. DNA was extracted from chorionic villi. DNA of the father was used as a control. Fluorescence labeled PCR and denaturating slab gel electrophoresis was used for allele length determination in this case since this method was more rapid. Analyses revealed that the fetus carried repeat blocks of 15 and 70 (±2) CAGs, respec-

tively, while - as expected - the mother carried two normal alleles (15 and 17 CAGs, respectively).

The fetus was therefore mutation carrier for HD. It was explained to the parents that such large expansions are more frequently associated with juvenile onset phenotypes and more severe disease course and progression (i.e. anticipation). The couple decided to have pregnancy termination [TOP] and the genetic counselor provided support in their decision making. The pregnancy was terminated based on the result of the affected fetus in the first trimester by dilation and curettage. Our genetic service continues to support the family subsequently considering assisted reproduction techniques like heterologous insemination and else (see below).

Discussion

Medical genetics, once the province of a relatively small number of specialists and still practiced by some self taught amateurs, is now moving into the mainstream of clinical medicine thanks to the tremendous advances in the identification of the molecular background of many genetic diseases. However, genetic medicine in both clinical and research setting faces difficult tasks. One of them is counseling pre-symptomatic individuals with family history of severe progressive diseases with late onset. The medical geneticist has to help the patient in deciding whether to have pre-symptomatic testing and whether to disclose information to the partner if the test result is positive. Counseling may have dramatic impact on the life choices of the tested individuals (if proven to be carriers of mutant genes) but also on their families (wives, husbands) including their reproductive choices (16). In this aspect counseling related to predictive testing is an important process that involves the patient, his/her family and the counseling team in a long lasting relationship. Sometimes counseling expands beyond the initial tasks and expectations because of the increasing demand of the patients for information and support.

With the rapid development of genetics the number of diseases whose molecular basis has been identified grows up constantly. In the group of late onset autosomal dominant disorders HD still remains a medical challenge. Appropriate genetic counseling is needed in every individual case. Family history can give valuable information about the clinical course of the disease in the particular family. In our case the propositus reported severe clinical manifestation of HD in his family (figure 1). His mother died in her 30s after committing suicide because of rapid progression of the disease. His aunt was also affected and died at relatively young age her death being related to the consequences of the disease. So, the patient's decision to have pre-symptomatic testing was motivated not only by curiosity but also by the perfect awareness of the nature of the disease, its clinical course and consequences. Contributions for developmental psychology and research on adolescents' decision making competence suggest that adolescents are able to make informed choices about their health and personal lives (17,18).

Predictive genetic testing also presents with unique issues in the legal and ethical debate concerning disclosure of information within the physician-patient relationship (19). In particular, in cases of severe progressive disorders with unfavorable prognosis it is a moral dilemma how to disclose the information to other family members. The awareness of the damaging effect of the disease can cause anxiety in the family. On the other hand, the disclosure of such information to the partner is particularly important in cases in which awareness of the test results might strongly influence further important life decisions including reproductive choices. Our patient had chosen to inform his wife about the positive test result and he received strong moral support from her. That made further genetic counseling of the couple easier.

Another important aspect in cases of positive predictive testing for late onset diseases is counseling couples regarding their reproductive plans. The couple must be aware of the opportunities for prenatal diagnosis and TOP in cases of an affected fetus. Information on the applicability of assisted reproductive technologies [ART] to prevent genetic disorders must be discussed with patients too. Depending on who is affected in the particular couple heteroinsemination or oocyte donation may be considered. At this stage of counseling obstetricians must also be involved to explain the potential advantages and risks of the different methods for invasive prenatal testing and TOP.

A considerable amount of research has studied both predictive genetic test decisions for HD and the impact on the individual of receiving a test result. The core of the process of testing has been defined by international committees several years ago (20) and these guidelines are still applicable. Our own experience with this kind of testing pointed out several important steps. Firstly, the evaluation of motives is an essential step before performing the test itself. Second, psychological assessments of depression and anxiety in individuals at risk, who want to be tested, should be part of the process. The test results provide the physicians with optimal means for counseling of the clients. Finally, presenting of the test results to the counselee must be preceded by psychological tests too. The rates of depression and anxiety should be less than critical, and if they are not, counseling should go on involving psychologists, until they reach acceptable levels for the patients.

The multi-disciplinary approach ensures that comprehensive assessment and appropriate expertise are available when ever required. Genetic services facilitate access to genetic counseling for at-risk relatives and follow-up of mutation carriers after predictive testing (21,22). Annual neurological assessment allows symptoms to be identified and treated early.

The reported case was the first one of predictive testing and pregnancy termination after prenatal diagnosis of a late onset autosomal dominant disease in Bulgaria. Certainly, it will be followed by others, since introducing

sophisticated molecular techniques in clinical practice will increase the number of tests available. The approach described here has to be considered in that regard.

In summary, pre-test and post-test genetic counseling is an important and essential process in contemporary medical practice (23). We were able to demonstrate that, given intensive multidisciplinary support, predictive testing can help people at risk for HD and their families cope with this extremely straining situation, even if DNA testing subsequently reveals unfavorable results.

References

1. Harper PS. The epidemiology of Huntington's disease. In: Harper PS (ed), Huntington's disease: Major problems in neurology; Vol 31. 2nd ed. Harcourt Brace 1996: 201-39.
2. Harper PS, Shaw D. Huntington's disease: genetic and molecular studies. In: Harper PS (ed). Huntingtons disease: Major problems in neurology; Vol 31. 2nd ed. Harcourt Brace 1996: 241-92.
3. Nance MA, Mathias-Hagen V, Breningstall G, Wick MJ, McGlennen RC. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. Neurology 1999; 52: 392-394.
4. Borbas T, Hegyesi H. Huntington chorea: genetics and biochemistry, diagnosis and therapy. Acta Pharm Hung 2002; 72(2): 127-36.
5. Hersch SM, Greenamyre JT. Huntington's disease. In: Current therapy in Neurology.
6. MacMillan J, Quarrell O. The neurobiology of Huntington's disease. In: Harper PS (ed), Huntington's disease: Major problems in neurology; Vol 31. 2nd ed. Harcourt Brace 1996
7. Quarrell O, Harper P. The clinical neurology of Huntington's disease. In: Harper PS (ed), Huntington's disease: Major problems in neurology; Vol 31. 2nd ed. Harcourt Brace 1996: 31-72.
8. Morris M. Dementia and cognitive changes in Huntington's disease. Adv Neurol 1995; 65: 187–200.
9. Burgess MM, Adam S, Bloch M. Dilemmas of anonymous predictive testing for HD – privacy vs. optimal care. Am J Med Genet 1997 Aug 8; 71(2): 197-201.
10. Hayden MR. Predictive testing for Huntington's disease: the calm after the storm. Lancet 2000; 356(9246): 1944-5.
11. Hersch S, Jones R, Koroshetz W. The neurogenetics genie: testing for the Huntington mutation. Neurology 1994; 44(8): 1369-73.
12. Chapman E. Ethical dilemmas in testing for late onset conditions: reactions to testing and perceived impact on other family members. J Genet Couns 2002; 11(5): 351-67.
13. Zung WW. A self-rating depression scale. Arch Gen Psychiatry. 1965;12: 63-70.
14. Taylor JA. A personality scale of manifest anxiety. J Abnorm Psychol. 1953; 48(2): 285-90.
15. Paspalanov I, Shtetinski D. The problem of the range of the anxiety and its measuring in psychology. Psychologia 1980; 2: 74-85.
16. Taylor SD. Predictive genetic test decisions for Huntington's disease: context, appraisal and new moral imperatives. Soc Sci Med 2004; 58(1): 137-49.
17. Binedell J, Soldan JR, Scourfield J, Harper PS. Huntington's disease predictive testing: the case for an assessment approach to requests from adolescents. J Med Genet. 1996; 33(11): 912-8.
18. Etchegary H. Genetic testing for Huntington's disease: How is the decision taken? Genet Test 2006; 10(1): 60-7.
19. Hakimian R. Disclosure of Huntington's disease to family members: the dilemma of known but unknowing parties. Genet Test 2000; 4(4): 359-64.
20. Guidelines for the molecular genetics predictive test in Huntington's disease. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea. Neurology 1994; 44(8): 1533-6
21. Elger BS, Harding TW. Should a suicidal patient with Huntington's disease be hospitalized against her will? Attitudes among future physicians and lawyers and discussion of ethical issues. Gen Hosp Psychiatry 2004; 26(2): 136-44
22. Nance MA, Ludowese CJ. Diagnosis of Huntington disease: model for a predictive testing program based on understanding the stages of psychological response. Am J Med Genet 1994; 52(1): 118-20.
23. Ensenauer RE, Michels VV, Reinke SS. Genetic testing: practical, ethical, and counseling considerations. Mayo Clin Proc 2005; 80(1): 63-73.

IMPLIKACIJE PRVE PRENATALNE DIJAGNOZE HANTINGTONE BOLESTI U BUGARSKOJ POSLE PREDIKTIVNOG TESTIRANJA

Ivanka I. Dimova[1], Stefan Wieczorek[2], Violeta G. Dimitrova[3], Albena Krasteva[4], Stoyan G. Lalchev[1], Draga I. Toncheva[1]

[1]Departman za medicinsku genetiku, Medicinski univerzitet, Sofija, Bugarska
[2]Ruhr–Univerzitet u Bohumu, Humana genetika, Nemačka
[3]Departman za fetalnu medicinu, Univerzitetska bolnica za akušerstvo i ginekologiju "Maichin dom" – Sofija, Bugarska
[4]Klinička pihologija, Univerzitetska pedijatrijska bolnica, Sofija, Bugarska
E-mail: dragatoncheva@yahoo.com

Kratak sadržaj: *Pitanje testova za gene Hantingtonove bolesti (HD) je kontraverzno. Pažljivo savetovanje i praćenje je potrebno ako se testiraju asimptomatski članovi porodice izloženi riziku. Iako su rezultati testova "crno-beli" u >99% slučajeva, njihova interpretacija može biti vrlo problematična i teška u pojedinačnim slučajevima. Iako je identifikacija HD mutacionog gena olakšala prediktivne testove, ne postoji odgovarajući tretman koji bi usporio ili promenio razvoj bolesti. Zbog toga su testovi vezani za brojne emocionalne, praktične i etičke probleme. Odgovarajuće genetsko savetovanje i podrška su neophodni u takvim slučajevima. Ovde predstavljamo naše iskustvo u testovima predviđanja HD, posebno naglašavajući suštinske korake u proceduri testiranja: evaluaciju motiva, psihološku procenu pre i posle testova i stalnu podršku pacijenta/para tokom celog procesa, kao i njihovih odluka o reprodukciji.*

Ključne reči: *Hantingtonova bolest, prediktivni testovi, ponovljena ekspanzija mutacija, genetski savet*