SELECTED SUMMARY

Screening for beta-thalassaemia

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Screening extended families for genetic haemoglobin disorders in Pakistan. Ahmed *et al. NEJM* 2002;**347:** 1162–8

In Pakistan, the autosomal recessive beta-thalassaemia gene is present in 5% of the population. The estimated birth rate of affected infants is 1.3 per 1,000 live births, and about 5,250 infants with beta-thalassaemia are born annually. A monthly blood transfusion maintains an excellent quality of life during childhood but leads to iron overload and death in adolescence or early adult life. The annual cost of chelation therapy with desferrioxamine, US$ 4,400 per patient, is prohibitive (10 times the average annual income).

In societies where most couples are unrelated, recessive genes run in families for many generations without manifesting. With a cultural preference for consanguineous marriage, when a gene for a recessive disorder is present in kindred, an affected child in at least one branch of the extended family is likely. Investigating extended families with the first child with a diagnosis becomes an alternative to mass screening for identifying couples at risk. The study was designed to test this hypothesis.

Fifteen families of children with beta-thalassaemia, one of a carrier and eight control families with no history of the disease were tested to identify carriers. Genetic counselling was conducted according to internationally accepted guidelines. A meeting was arranged with key members (in affected families, usually the parents of the child with the index case) for the test. Results were given to the carriers themselves (or to the parents when a carrier was <15 years of age). The meaning of carrier status, the importance of knowing whether or not one's partner was a carrier, the availability of prenatal diagnosis, and (for those unmarried) the importance of test results when planning marriage, were explained.

No carrier was found among the control families. In the affected families, 31% were carriers who had a risk if they married another carrier, resulting in a 25% chance of having a child with beta-thalassaemia. In 8% of the cases, both were carriers.

During a four-year follow up, there were seven new marriages and engagements. Family members said that test results were taken into account. Four consanguineous couples were known not to be at risk; in three, one partner was a known carrier and in one, the man was a known non-carrier, so the woman was not tested. One consanguineous couple who had not taken part in the study came spontaneously for premarital testing and was found not to be at risk.

Two men who were carriers were marrying more 'distant' women who had not been tested (a second cousin in one case, and the other marrying within the *biradri* [community]). In one, with three previous broken engagements, the potential problem was not disclosed. In the other, when two engagements were broken on disclosing the carrier status, it was not mentioned during the third engagement, and the bride was found not to be a carrier.

Till date, no couple at risk with two or more healthy children has undertaken a further pregnancy, and seven prenatal diagnoses have been performed for six couples at risk with no, or only one, healthy child. A couple that was prospectively identified as at risk and that had one unaffected child declined prenatal diagnosis for religious reasons and had an affected child.

Commentary

The authors contended that 'The proposal that consanguineous marriage should be discouraged in such communities on genetic grounds is ethically unacceptable; it is also unrealistic, because more than 90% of marriages occur within the biradri and logically would have to be discouraged. Such a wholesale attack on a social structure has no chance of success.'

At first blush, it appears that individual autonomy is being carried to an extreme. If a particular action will lead to a deleterious outcome, shouldn't everything possible be done to prevent it?

The World Health Organization's (WHO) report on genetic counselling cited in the article (1) has an extensive discussion on the ethical dilemmas and choices available

to people with recessive genes for medical diseases in communities that practise consanguineous marriages. According to this report, based on beta-thalassaemia in the Eastern Mediterranean countries, information about carrier status has little effect on individual choice of partners. This may not apply to India and Pakistan where most of the marriages are arranged. Observations of the WHO suggest that close relatives accept marriage with a carrier more easily than unrelated persons.

Professional ethical practice in genetic counselling, as it has gradually evolved during the past 20 years, can be summarised under three simple headings: the autonomy of the individual or couple; their right to complete information; and the highest standard of confidentiality.

Genetic counselling should be non-directive, and that the genetic counsellor's main role is to provide full information, give the patients time for consideration, and support them in making the decisions they feel to be morally right for themselves. Genetic counsellors may also assist in the evolution of public attitudes by reporting their patients' views and choices back to society.

Couples at risk detected by premarital screening

We understand little of how most arranged marriages come about to make any valid assumptions about the effect of genetic information on choice of partner. In all societies, marriage is a complex social interplay of personal preference, family considerations and social traditions.

It often seems that beta-thalassaemia can be prevented if couples at risk are identified before marriage, on the assumption that they will then decide to separate and each find another, non-carrier partner. This may be possible in a developed country such as Greece or Italy, but in a developing country such as India or Pakistan, it is likely to lead to a marriage with another for the man but the woman may have a hard time finding another mate. Research data are needed on the frequency of this choice, its relationship to the approach adopted for counselling, and the short and long-term effects on individuals and families. Questions that need to be answered include the extent of the social stigma that rearranging a planned marriage can cause for young people and their families, and the risk of the problem recurring because the new partner is also a carrier. This risk is not insignificant: if population carrier frequency is 6%, the chance that one or other of the new partners is a carrier is 12%—even higher if the new partner is a relative.

A second possibility is to marry as planned, but avoid having children altogether. This choice is particularly difficult in strongly family-centred societies. It is also technically difficult unless high-quality contraceptive assistance is readily available. If a couple at risk gets married and conceives a child, even if the expensive foetal testing were made available, religious and social mores may not favour prenatal testing and abortion.

This article is about the genetic inheritance of thalassaemia—an autosomal recessive disease. Congenital disorders with different inheritance patterns may pose different dilemmas.

Couples at risk who are already married

A choice to have no more children may be easier for couples who already have healthy children, but is extremely difficult for those whose children are affected. The husband may be under pressure to take a second wife to ensure healthy children. The decision to have no more children also requires access to reliable and highly effective contraception that may not always be available, especially in rural areas.

Another option is to continue to have children and take the risk. In the absence of prenatal diagnosis and ready access to family planning, this was the only option available to most families until recently and this may be the only option in most rural areas of India and Pakistan. Some may feel that this is the path God has laid down for them. Options such as artificial insemination by donor, egg donation or adoption, have not proved popular in any society.

Widespread dissemination of genetic risks associated with consanguineous marriages through public information campaigns may discourage such marriages. However, pressure against cousin marriage rarely alters what people actually do, although it can make them feel uncomfortable about it. Even where consanguineous marriage is common, most couples have perfectly healthy children. The advice against marriage to a first cousin because their children may be born sick causes confusion and loss of confidence in medical advice. Also, fear of criticism of social conventions may prevent some from seeking genetic counselling.

This article points to a cost-effective strategy for identifying carriers of the beta-thalassaemia gene. A patient and persistent public health approach will be required to eradicate this disease. This has happened in Cyprus and we hope it will happen in Pakistan and India as well.

Reference

1. Alwan A, Modell B. Community control of genetic and congenital disorders. Alexandria, Egypt: WHO Regional Office for the Eastern Mediterranean, EMRO technical publication series 24, 1997. Available online at www.emro.who.int/Publications/EMRO%20Pub-TPS-GEN.htm.