Thalassaemia control by carrier screening: The Indian scenario

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Thalassaemia control is possible by screening of general population for carrier status and antenatal diagnosis in couples identified to be at risk (possibility) of having a child with thalassaemia. We conducted a study to explore if extended family screening for carrier detection was feasible in India and what are the barriers to its acceptance. For this, 100 families with a thalassaemic child were interviewed using a predesigned questionnaire. Results show that although parents have no reservation in sharing information about their thalassaemic child, relatives of 62 parents accepted the risk of being a carrier and 14 families got themselves tested for it. Thirtyfour families were willing to get tested but because of non-availability of screening facility in the nearby town, they could not get themselves tested. We conclude that there is need to make screening more readily available and motivate the high risk groups through awareness programmes.

β-THALASSAEMIA major (TM) is the commonest lethal single-gene disorder in India with a prevalence of 1–17% in different population groups. The mean prevalence is 3.3% (refs 1–5). TM is usually diagnosed at infancy and is characterized by ineffective erythropoeisis, bone-marrow expansion and rapid destruction of erythrocytes. Anaemia demands frequent blood transfusion to maintain life, while haemosiderosis and other complications of the disease require a continuous and distressing treatment regime that includes iron chelation treatment, regular medical supervision, frequent admissions to the hospital and on many occasions, surgery. If left untreated, the affected children die of heart failure in early childhood. The only curative treatment available for this disease is bone-marrow transplantation which is expensive and not easily affordable by a common Indian family. Consequently, the cost of supporting a thalassaemic child varies from few thousand rupees to a lakh per year depending upon the kind of treatment opted by the parents. Therefore, the only option is to prevent the birth of an affected children by increasing awareness among the masses. Prevention can be primary and secondary. Primary prevention means preventing the birth of thalassaemic children in the general population. This is possible by screening the carrier status (Hb A_2) of the general population or by screening all pregnant women. Secondary prevention means preventing birth of another child in a family with an affected (thalassaemic) child. For this, extended family screening (EFS) can be useful.

The homozygous state of β-thalassaemia has a spectrum of clinical severity. The disease is inherited as an autosomal recessive condition, which means that both the parents of the affected child are carriers of the gene. Carriers of this gene are symptomless. The carrier couples have 25% risk of having an affected child in each pregnancy. Since parents of affected children are carriers, there is, therefore, a strong possibility that their relatives (sibs of parents and consequently their children) may also be carriers of the thalassaemia trait, i.e. they may also be carriers of the thalassaemia gene (heterozygotes). In other words, relatives of a TM child can be said to be at a high-risk of being carriers. If carriers marry carriers, then in each pregnancy there is a 25% chance of their giving birth to an affected child. The carrier status of the relatives can be known by screening for thalassaemia. This concept is broadly known as EFS. Prenatal diagnosis, which is available at many centres in India, can be offered to all at risk pregnancies (chorionic villus sampling done at 11–12 weeks of gestation) to know whether the foetus is affected or not.

Among heterozygotes of haemoglobinopathies, higher fertility has been observed than among homozygotes[6,7], which implies that heterozygotes (carriers) produce more children than normal or homozygotes of the defective gene, to compensate for the loss due to elimination of homozygotes. This leads to higher frequency of heterozygotes in the population. Prevalence of consanguinity is variable in Indian population groups. However consanguinity compounds the situation, as it is an important issue in the spread of this disease. In India it is estimated that there are over 25 million carriers of this disease and approximately 8000 thalassaemic babies are born every year. In other words, thalassaemia is a major problem of the society, as even the best of treatments is not free from complications. Hence, the only effective strategy to control the incidence of thalassaemia is to prevent the

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birth of thalassaemic children, and for prevention the key step is carrier-screening[8,9]. Advances in biotechnology and molecular biology have made carrier detection and prenatal diagnosis of TM possible, and the effectiveness of these advances is visible by 10–20-fold reduction in TM children in Cyprus, Greece, Italy, Sardinia and UK[10].

Our experience has shown that in majority of the cases, whether literate or illiterate, relatives of thalassaemic children do not come forward for carrier detection test despite repeated genetic counselling. This year, one couple who had an affected child on regular blood transfusion gave birth to another affected child, as they did not opt for prenatal diagnosis. Similarly, among first-degree relatives (sibs) of the parents of affected children there have been births of thalassaemic children. By screening these families which come under the high-risk category, it is possible to prevent the birth of affected children which is more cost-effective compared to screening the general population in the Indian context. It was for this reason that the present study was undertaken (to explore the feasibility of EFS). The first objective of the study was to evaluate whether the parents share information about their thalassaemic child with their relatives, and the effectiveness of these parents in communicating to their relatives the increased risk of having a thalassaemic child (and therefore their co-operation and help in making EFS possible). The second objective was to evaluate the attitude and response of the relatives towards EFS. If they did not accept EFS, then what were the barriers to its acceptance?

Material and methods

The study was conducted at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow between 1998 and 1999. There are 110 TM patients registered for the hypertransfusion programme and iron chelation therapy. A large number of patients come from Sindhi, Muslim and Punjabi communities which come under the high-risk group, as thalassaemia trait is highly prevalent in these communities. Patients visit the hospital every 3–4 weeks for blood transfusion. The patients belong to Uttar Pradesh, Bihar and Punjab and come from low, middle and high socio-economic strata (which reflects on their literacy level also). Parents (couples) of 100 thalassaemic patients were interviewed to evaluate how well they understood thalassaemia as a genetic disorder, and the risk of its recurrence among their relatives. Since most of the patients come from outside Lucknow, they are accompanied by both the parents. However, it is not possible for the relatives of the parents to accompany them to the hospital because of the distances involved and financial reasons. Hence the relatives were not interviewed directly (instead the parents were interviewed). The following selection criteria were used to include the parents in the study: (i) parents had sibs who had not completed their families and, therefore, were at risk of giving birth to a TM child, and (ii) sibs had children who were of marriageable age and were at risk of giving birth to a TM child, if they were carriers of the TM gene.

The parents were counselled repeatedly (over years) on increased risk of their relatives being carriers of the thalassaemia gene and consequently the need for EFS. Parents were provided literature (in Hindi) on thalassaemia for distributing it among their relatives (sibs), to increase their awareness regarding the disease.

Prior to the interview, the parents were given a brochure containing complete information on thalassaemia as a disease, its incidence in the general population and high-risk groups, treatment and prevention. In the structured interview, the parents were asked: (i) whether they had informed their families (sibs, first and second cousins), friends and co-workers that they were carriers of the thalassaemia gene and therefore had a thalassaemic child; and (ii) whether they were aware of the increased risk of their family members being carriers and capable of having a thalassaemic child; (iii) whether they had informed their relatives about the availability of antenatal diagnosis for carrier couples, and (iv) whether parents had any reservation in our approaching their relatives directly to counsel them on their increased risk of being thalassaemia carriers and regarding the availability of carrier detection test. To evaluate the attitude of the relatives towards the above-mentioned information, the parents were further asked (i) whether their relatives accepted the increased risk of being carriers and of having a thalassaemic child, (ii) if so, whether they were willing to get screened or had they already got tested, and (iii) if their response was negative, then what were the reasons or barriers in getting their carrier status tested?

Results

Parent's attitude

Out of 100 parents (couples), 96% had no reservation in sharing information about their thalassaemic child. Four per cent who were hesitant in sharing information about their thalassaemic child with others gave the following reasons: (i) they considered thalassaemia as a social stigma which could affect their image in the society, leading to social isolation and eventually affect the future marital prospects of other normal/carrier unmarried children in the family; and (ii) the relatives were illiterate and from a rural background, and therefore would not be able to understand the seriousness of the disease; (iii) the

husband and parents-in-law often blamed the wife for the disease in the child. Out of 100 couples, only 2 families had objections in our approaching the relatives directly for genetic counselling, as they wanted to be highly secretive about their child's disease.

Relative's attitude (N = 96 couples)

Relatives of 62 couples (64.5%) accepted their increased risk of being carriers while the remaining did not accept that they could be carriers of the gene (Figure 1). Out of 62 couples, sibs of 56.4% (35 families) were willing to get their carrier status tested and 22.5% (14 families) had already got themselves tested, because they were educated and feared recurrence in the family. The following reasons were given by the parents for their relatives not getting carrier status tested: (i) relatives did not take the information about their increased risk of being carriers and having a thalassaemic child seriously, (ii) relatives had already completed their families and all of them had normal children, and (iii) test for carrier detection was neither available in the towns where they were living nor in the nearby towns.

Discussion

Primary prevention based on a combination of increased awareness of the general population, carrier screening, genetic counselling and prenatal diagnosis, has led to almost total elimination of TM children in Cyprus, and to a considerable extent in Greece, Italy and Sardinia[11,12]. Therapeutic protocols are still beyond the reach of the vast majority of patients and families in India. Information available to the parents on thalassaemia is hospital-based. The control and prevention of such a disorder is, therefore, of immense importance. The most important requirement for implementing awareness or control programmes for any disease is to bring about awareness among the masses (i) about the disease, (ii) how it spreads, and (iii) how it can be controlled.

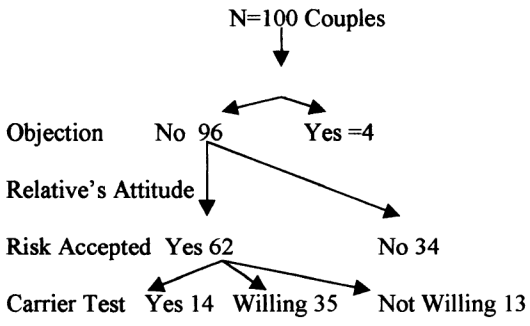

Figure 1. Algorithm of attitude of the relatives.

Community screening is an important component of identifying carriers in the country. Whether carrier screening should be done at school or college level, before or after marriage or during pregnancy is debatable. Premarital screening attaches a stigma to the carriers, which can blight the prospects of marriage.

Prenatal diagnosis is an important way of preventing birth of thalassaemic children. For this, characterization of DNA mutation of β-thalassaemia in the family is important. If thalassaemia is to be controlled, then at the regional level prenatal diagnosis centres, facility for medical termination of pregnancy should be established. If regional centres are few, then there should be collection points or centres for collection of samples of CVS, which can be transported to central laboratories.

Genetic counselling is an essential component of the strategy for control and prevention of haemoglobinopathies to creating awareness of the disease and its burden on the family and society. Genetic counselling (prospective and retrospective) for high-risk couples and communities is the most important medical advice to be imparted[10].

Management of thalassaemia through preventive, promotive and curative methods is important[13]. The prerequisite for a successful prevention programme is health education, public awareness and sensitization, and screening of the population for identification of heterozygotes or carriers[14].

The reason that prompted us to conduct the study was the birth of TM children (recurrence) in four different families of the relatives (sibs) of parents with a TM child. This happened in spite of us repeatedly counselling the parents regarding increased risk of their relatives (sibs) being carriers and consequently capable of giving birth to a TM child. These parents were asked to get the carrier status of all the first-degree relatives tested. Another couple who had a thalassaemic child (registered with us for hypertransfusion and iron chelation therapy) gave birth to another thalassaemic child last year as they did not opt for prenatal diagnosis, despite repeated counselling. Birth of this child could have been prevented as the mutation of the affected child and those of parents were known.

This study was designed to evaluate the possibility/feasibility of preventing/controlling the birth of TM children in high-risk population through EFS.

Results of this study show that although majority of the affected families have no reservations in sharing information about their thalassaemic child with their relatives and friends, there is low acceptance (64%) among relatives of the increased risk of being carriers and having thalassaemic children. This low rate of acceptance and indifferent attitude towards detection of carrier status may be due to lack of first-hand experience of raising a thalassaemic child who is a social and

financial burden on the family. To add to this, there was an element of fear of the unknown. Further, because a lot of relatives had completed their families, they were not able to comprehend the fact that the carriers are symptomless and their children, if carriers, were at the risk of having a thalassaemic child in future; hence this indifferent attitude. However, in families where there has been an incidence of recurrence, there is good acceptance of secondary prevention.

Our results are supported by comparative studies on Indians and Cypriots, which show that there is an appreciable difference (in attitude) between the two in the acceptability of genetic counselling and antenatal diagnosis for thalassaemia[15]. Compared to Indians, there is an overwhelming demand for this service from the British Cypriot community and a resultant reduction in the number of normal pregnancies terminated. The difference in demand (visible in terms of rejection of information) for carrier detection and antenatal diagnosis for thalassaemia as well as sickle-cell anaemia is striking in the case of the Indian compared to other populations[16]. Cypriots are distinguished from other groups studied by a high level of awareness of TM among health workers and the community.

Historically, TM has been seen as a problem for the Mediterranean population and concerted awareness campaigns have greatly reduced its birth prevalence in the Mediterranean area[14]. In Cyprus, there are now almost no new affected births[15]. Usually, it is thought that migrated Indian families have a broader outlook, but these studies show that Indian families living abroad have very strong cultural attitudes.

For a community with such an attitude (which could be cultural), the only alternative to prevent birth of thalassaemic children is to firmly press in thalassaemia control programmes. The main objective of such programmes should be to bring about awareness among the masses through community and health education, in order to motivate high-risk groups for carrier screening (Figure 2). EFS should be the main focus of these programmes, since the first-degree relatives of a thalassaemic child have 14% higher risk of having an affected child compared to the general population. Family physicians and obstetricians can play an important role in motivating the high-risk groups. Screening of pregnant women along with their spouses should be made compulsory and free of cost. Genetic disorders, especially thalassaemia and the

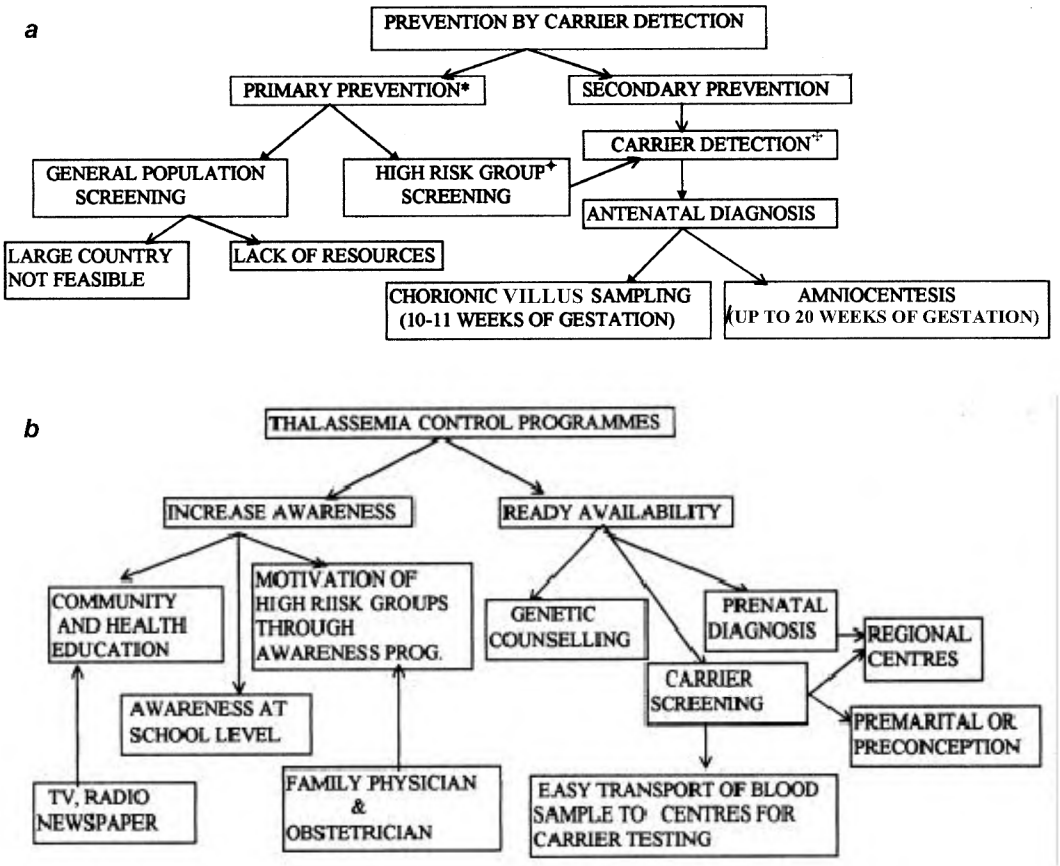

Figure 2. *a*, Prevention of TM by carrier screening. *Prevent birth of first TM child in family; +Prevent recurrence in family and relations; ✦Families with one TM child in relation and population groups with high frequency of β-thalassaemia gene. *b*, Prevention of birth of thalassaemic children by extended family screening in the Indian context.

like, should become a part of curriculum at the school level, which will facilitate erasing the image of this disease as a social stigma (as the public will be more adapted to hearing and knowing about the disease).

Emphasis should be laid on the modes of communication for information, and to make such information effective, it must be adequately supplemented with audio-visual coverage, because without personal experience, the seriousness of the situation cannot be appreciated. Facilities for genetic counselling, carrier detection and antenatal diagnosis should be made readily available. This might require opening up of new centres all over the country. For this, financial support can be sought from major international agencies with cooperation from both, the government and communities in emerging countries[15]. In places where carrier screening test is not available, provision should be made for collection of blood samples and their transport to centres for carrier testing. Selective termination of affected foetuses should not be considered a taboo.

In view of high cost of treatment (Rs 125,000 per year per patient) involving 20–30% of total family income on medical treatment[17] besides physical trauma, frequent absence from school or work for blood transfusion, and psychological harassment to patient and families, preventive genetic strategies for thalassaemia are of utmost importance in the Indian context.

The most effective approach to reduce burden of the society is to reduce the incidence by implementation of a carrier screening programme offering genetic counselling, prenatal diagnosis and selective termination of the affected foetuses in India[10].

Three main messages that need to be propagated are: (i) the carrier state has no disadvantage, (ii) the homozygous state is very severe and fatal, (iii) prenatal diagnosis is available and safe[9].

More studies need to be carried out at different centres in India in order to find the reasons for not accepting EFS. At present, there are no studies on feasibility of EFS for controlling thalassaemia in the Indian context.

Conclusion

Diseases which are known to run in families and have high-risk of recurrence become a social stigma when nothing or very little is known about them. Illiterate populations are ignorant about the medical, social and financial burden of the disease. This further compounds the problem. Primary prevention of TM disease is possible by carrier detection and the availability of antenatal diagnosis. In preventing this disease, the attitude of the population at large and those of families directly involved in the care of affected children are of prime importance. Cyprus, Greece, Italy and Sardinia are excellent examples demonstrating the effectiveness of control programmes for prevention of birth of TM children. In the Indian context also prevention of thalassaemia is possible only by bringing about sensitization at individual, social and state levels.

1. An Indian Council of Medical Research Task Force Study, Indian Council of Medical Research, New Delhi, 1993.
2. Modell, B. and Bulzhenov, V., *World Health Stat Rep.*, 1988, **41**, 209–218.
3. Sukumaran, P. K., in *Trends in Hematology* (ed. Sen, N. N.), Kolkata, 1975.
4. Verma, I. C., Choudhary, V. P. and Jain, P. K., *Indian J. Pediat.*, 1992, **59**, 649–645.
5. Marwaha, R. K., *Indian Pediat.*, 1994, **31**, 267–271.
6. Balgir, R. S., Dash, B. P. and Das, R. K., *Indian J. Pediat.*, 1997, **64**, 79–84.
7. Balgir, R. S., *ibid*, 1996, **59**, 449–454.
8. Wong, C., *Ann. Acad. Med. Singapore*, 1985, **14**, 654–665.
9. Kabra, M., *Natl. Med. J. India*, 1999, **12**, 198–201.
10. Balgir, R. S., *ibid*, 1999, **12**, 234–237.
11. Cao, A., Furbetta, M. and Galanello, R., *Am. J. Hum. Genet.*, 1981, **33**, 592–605.
12. Cao, A., Rosatelli, M. C. and Galanello, R., *Curr. Opin. Genet. Dev.*, 1991, **1**, 48–53.
13. Balgir, R. S., *Anthropology, Population and Development* (ed. Sharma, J. C.), Inter-India, New Delhi, 1995, pp. 151–171.
14. Balgir, R. S., *Indian Pract.*, 1996, **49**, 219–226.
15. Weatherall, D. J., *Ann. N. Y. Acad. Sci.*, 1998, **850**, 1–9.
16. Modell, B., Ward, R. H. T. and Fairweather, R. H. T., *Br. Med. J.*, 1980, **280**, 1347–1350.
17. Sangani, B. *et al.*, *Bull. W.H.O.*, 1990, **68**, 75–81.

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