Paper

Thalassaemia control in developing countries - the Sri Lankan perspective

D M D Perera¹, D Gunasekara², A Wijekoon³ and M Petrou⁴

Ceylon Medical Journal, 2000; **45**:12-16

(Key words: Prevention, prospective screening, genetic counselling)

Abstract

Beta thalassaemia is a Mendelian recessive disorder. The economic and social cost of the disease is high due to patients' life long need for monthly blood transfusions and treatment with desferrioxamine, an iron chelating agent. Wider availability of cheaper drugs is on the horizon. If there is no concomitant reduction in the number of new thalassaemia major births, there will be a cumulative increase in numbers requiring treatment. The frequency and severity, and the economic and social costs of thalassaemia, support the case for the introduction of a carrier screening and counselling program in Sri Lanka. A three-pronged plan emphasising professional, political and public education is outlined.

Introduction

Beta thalassaemia is a Mendelian recessive disorder which affects the synthesis of β globin chains of the adult haemoglobin molecule, HbA (1), prevalent in Mediterranean, middle eastern and Asian countries. Thalassaemia major patients require regular blood transfusions and removal of excess iron by subcutaneous infusion of desferrioxamine. The World Health Organisation has estimated that an annual average consumption of 27 units of blood and Rs 400 000 worth of the drug are needed to manage each patient according to recommended standards (2). In a resource limited environment it is difficult to meet these demands, and patients often suffer iron overload induced organ damage. Survival rates beyond the second decade are low. At Rs 1 to 2 million for a bone marrow transplant (India, UK and Italy), a permanent cure is also out of reach for many patients (2). A more economical orally active chelator, Deferiprone, is available but there is still debate over its efficacy and safety (3, 4, 5). At an annual expenditure of about Rs 125 000 for each patient, thalassaemia represents an enormous drain on health care budgets. Despite the significant burden on the state's economic and social resources, Sri Lanka still has no comprehensive thalassaemia control program.

The problem

There are about 1000 β thalassaemia major patients in Sri Lanka (6), with an estimated annual homozygous birth rate of about 100 (2). Many are born to parents who had no previous knowledge of their carrier risk. Last year our pilot study showed that less than 1% of the population in Colombo had heard of thalassaemia (7). Awareness may have improved since then, with the publicity over the shortage of Desferal (6), but further efforts are needed to increase clinical, political and public awareness of thalassaemia. The availability of cheaper iron chelation will prolong patient survival and if there is no concomitant reduction of new cases, the cumulative number of patients needing treatment will rise. Hence immediate action must be undertaken early to prevent thalassaemia becoming a major health and economic burden in the future. The social and economic costs of the disease support the case for commencing a carrier screening and counselling program in Sri Lanka.

Globally thalassaemia control has been achieved with public education, carrier screening, counselling, prenatal diagnosis and selective termination of affected fetuses (2). The most successful preventive program have been developed appropriate to the needs of the community, and sensitive to their cultural and social identity (8). At present the resources and expertise for prenatal diagnosis are unavailable, and termination of pregnancy is not legal in Sri Lanka.

Sri Lanka is an island, small in size, with a relatively small population. There is also relative uniformity in ethnic origin ie. south Asian. The adult literacy rate is 90% (9), a great boon to promote public awareness. Some 30 years ago, Cyprus was in a similar situation. Now it is often heralded as the success story in thalassaemia control. Cyprus has a thalassaemia carrier rate of 16%, but within 30 years the annual homozygous birth rate has

¹Clinical Scientist, Department of Obstetrics and Gynaecology, Royal Free and University College, London, ²Paediatrician, Sri Jayawardenepura University, Nugegoda, ³Paediatrician, University of Peradeniya and ⁴Head of Perinatal Unit, Department of Obstetrics and Gynaecology, Royal Free and University College, London, UK. (Accepted November 13, 1999).

been reduced to almost zero through population screening, genetic counselling and prenatal diagnosis (10).

Prevention

A prevention program needs the support of a 'grand alliance' of three parties (11) - the people, policy makers and health professionals. The public must be sensitised, political leaders must be shown evidence of benefit and professionals must take an active role in campaigning for appropriate infrastructures within the health service. Who should initiate it? It has to start with the clinician. The paediatricians or physicians treating thalassaemia patients are close to the patient's family. They are able to collaborate with other professionals, have access to policy makers to advocate political change, and hence best equipped to lead preventive programs in their institutions.

Worldwide campaigns have been undertaken with patient and parent support groups (12). These groups often consist of highly committed individuals. They are capable of strengthening and empowering people to effect social and political change. Sri Lanka has many such organisations and health care professionals can achieve much with their support. Since carriers of β thalassaemia are to a large extent asymptomatic, motivating a healthy person to undergo a blood test depends heavily on the strength of the awareness campaign. Increasing public awareness will also help remove myths, fears and anxieties about genetic disorders in general, and help to draw attention to the patients' needs, such as safe blood transfusions.

Screening

A genetic population screening program is a systematic effort to identify and counsel as many people as possible in the community at risk, ideally before they produce an affected child (2). It is important that screening is undertaken voluntarily. Volunteers must know why they are being screened and give informed, written consent. There are many approaches to screening. Selective screening of close relatives of an affected child is one of the most cost effective ways of identifying carriers. A study conducted in Pakistan showed that family screening can enhance carrier detection efficiency several fold over random screening (13). In our pilot survey of random population screening the carrier frequency was found to be about 2% for β thalassaemia (7). Another route for obtaining a high yield of carriers is to screen a whole village or a district.

The age of screening is an important consideration: as a child, premaritally or as a parent. Each has its advantages and drawbacks. The advantages of screening at school age are the availability of a wider range of reproductive options, the possibility of incorporating information into the school curriculum and the opportunity of screening a significant number of future parents. The

disadvantage is that if done too early the impact of the knowledge may get lost before adulthood is reached (14,15).

Premarital screening has been performed in Turkey (16) and it is the national policy in Greece (2), Cyprus (17) and parts of Italy (2). Identified at-risk couples are given advice on reproductive options before marriage. There is no published evidence that a higher proportion of Sri Lankan thalassaemia major children are born to consanguineous parents. Consanguineous marriage is an important social custom in many societies for generations. In some communities it forms an integral part of the social structure and builds family unity (18). It is better to advocate thalassaemia screening before marriage to all, consanguineous or otherwise. Identified carriers can then be counselled individually.

Opportunistic screening, when parents come into contact with health care personnel for other reasons, is another way of detecting carriers. Well-baby clinics, and immunisation or family planning clinics are examples. The disadvantage is that if both partners are carriers it will limit their reproductive options. If the couple already have the desired number of healthy children, they may decide not to take a chance with another pregnancy.

A simple primary screening test of a full blood count and red cell indices, performed with an electronic cell counter will identify the majority of subjects at increased risk. Those with microcytic or hypochromic indices are tested with a secondary examination, quantitative analysis of HbA_2 . The key feature of β thalassaemia carriers is that they have raised HbA_2 levels. The results of our pilot survey showed that an MCH of < 77 pg, and MCV of < 27 fl and a HbA_2 level above 3.5%, as measured by high performance liquid chromatography (HPLC) were indicative of thalassaemia carrier status in adults (7). Haemoglobin A_2 can also be quantified using electrophoresis or column chromatography (2).

One problem with the above screening protocol is that microcytosis and hypochromia are also observed with more common disorders such as iron deficiency anaemia and α thalassaemia trait, a generally harmless condition is south Asians (18). Some types of α thalassaemia can be difficult to diagnose even with molecular biological techniques. A carrier detection protocol based on a primary screen of microcytic and hypochromic indices will also miss certain rare types of silent β thalassaemia carriers, those with MCV, MCH and HbA_2 values in the normal range (19), and those with certain structurally abnormal haemoglobins such as HbE (20), HbS (21), and HbD-Punjab (22) which have been reported in Sri Lankans. They may, in combination with each other or β thalassaemia genes, produce a severe disease (23). The use of DNA technologies may be appropriate in making a definite diagnosis in certain cases (24).

Diagram: Scheme for a preventive program for β thalassaemia in Sri Lanka

Counselling

Having identified the carriers, the task of recalling and counselling should be undertaken. It is important to preserve confidentiality and to inform all volunteers of their results. This relieves anxiety in non-carriers and provides an opportunity to counsel the carriers. If a definite diagnosis cannot be reached this should be clearly conveyed to the subject. If iron deficiency is found supplementation should be offered and the individual retested after the appropriate interval. If β thalassaemia trait is identified, genetic counselling should be undertaken, including the evidence that carriers of β thalassaemia have a diminished cardiovascular risk (25) and malarial risk (26). Carriers who are given this information together with the news of their carrier status have been shown to have a much more positive attitude towards their carrier status than others (27). Carriers should also be encouraged to bring other members of the family for screening and most important of all, to have their future marriage partner screened. Carriers, right to autonomous choice of marriage partner should always be respected (28). There are several published booklets (2,12,18,29) and information on websites (23,30) which can help. Nurses and other health care professionals can be trained to become genetic counsellors.

What the most realistic preventive strategy for the reduction of thalassaemia births in Sri Lanka might be is yet unknown. Pre-marital screening of relatives of thalassaemia major patients can be undertaken initially to find out if knowledge of carrier status influences choice of partner and their views on prenatal diagnosis. An action plan focussing on education, educating members of the index family, the public and policy makers, and other health care professionals is given in the diagram.

The first step is to offer screening to the patients' unmarried relatives of reproductive age. Once screened, those testing negative can be reassured and carriers can be offered reproductive counselling. The importance of marriage partner testing can be conveyed at this time. If the future partner is found to be a carrier, the range of reproductive options available must be clearly explained to enable them to make an informed choice. These are, not to marry another carrier, marry and take the chance of having children, adoption, donor insemination or seek prenatal diagnosis abroad.

Education

The second objective is to educate the public and convey the need for prevention to politicians. The ultimate success of a prevention program depends heavily on political will and commitment. Calls for assistance from influential policy makers to support the program need to be vigorously pursued, by creating awareness that β thalassaemia is a public health problem, that expenditure will continue to rise if urgent control measures are not taken,

and that a relatively small investment at this stage will provide substantial benefits in the future.

Educating health care professionals in genetic disorders should be undertaken, and incorporated into existing medical and nursing curriculums with refresher courses for those already in practice. A thalassaemia patient register must be maintained at each centre to establish epidemiology and to facilitate auditing. A national thalassaemia register should be established to collate data from all regions. Information such as age at diagnosis, number screened, number of carriers detected, and number of new thalassaemic children born can measure progress.

Data regarding many aspects of thalassaemia in Sri Lanka, such as epidemiological data on gene frequency are inadequate. The list also includes bone, endocrine and immunological aspects. Studies on safety, efficacy and acceptability of the oral chelator are essential. There are a number of international organisations that can be approached for support (31,32). International collaboration is vital for progress in research.

Sri Lankan health services are committed to primary health care. The outcome of the immunisation program is clear evidence of its success. It would be ideal if a comprehensive preventive program for β thalassaemia appropriate for Sri Lanka can also be incorporated into these services soon.

Acknowledgements

We are grateful for the support given by the Winston Churchill Memorial Trust, Beckman-Coulter, Merck International, University College, London, and the Ministry of Health and Indigenous Medicine, Sri Lanka.

References

1. Weatherall DJ: ed. The Thalassaemias. Methods in haematology. London: Churchill Livingstone; 1983.
2. Modell M: ed. Guidelines for the control of haemoglobin disorders. WHO Hereditary disease programme, 1994.
3. Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA. *et al.* Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassaemia major. *New England Journal of Medicine* 1998; **339**: 417-23.
4. Cohen A, Galanello R, Piga A, Vullo C. A multi-center safety trial of the oral iron chelator deferiprone. *Annals of the New York Academy of Sciences* 1998; **850**: 223-6.
5. Lucas GN, Perera BJC, Fonseka EAN, De Silva DDS and Fernandopulle M. A trial of deferiprone in transfusion-de-

- pendent iron overloaded children. (Abstract). Proceedings of the Sri Lanka College of Paediatricians, 3rd Annual Scientific Congress, 1999: FP24.
6. Sriyananda S. Life saving drug in short supply. *Observer, Sri Lanka*: 1999, 27 June. web site: <http://www.lanka.net/lakehouse/1999/06/27/new15.html>
7. Perera DMD, Gunasekera D, Wijekoon A, Bogammana K, Lokugamage A, Petrou M. Hereditary haemoglobin disorders and iron deficiency anaemia in city dwelling Sri Lankans. (Abstract). The 7th International Conference on Thalassemia and the Haemoglobinopathies, Bangkok, Thailand, 1999: T037.
8. Cao A, Rosatelli MC. Screening and prenatal diagnosis of the haemoglobinopathies: *Balliere's Clinics in Haematology* 1993; 6: 263-86.
9. Information provided by the Embassy of Sri Lanka in the United States of America. gopher:/inix.utexas.edu:70/00/asnic/southasi/Sri/srilanka
10. Petrou M, Modell B. Prenatal screening for haemoglobin disorders. *Prenatal Diagnosis*. 1995; 15: 1275-95.
11. Health Education: The Grand Alliance (keynote address). Report of the 13th World conference on health education, Houston, 1988.
12. Thalassemia International Federation, PO Box, 28807, 2083 Nicosia, Cyprus.
13. Ahmed S. An approach to prevention of thalassemia in Pakistan: A Muslim country. PhD thesis: University of London; 1998.
14. Mitchell JJ, Capua A, Clow C, Seriver CR. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and β -thalassaemia disease carriers in high schools, *American Journal of Human Genetics* 1996; 59: 793-8.
15. Oliva BE, Cladera SA, Torrent QM. Campaign for the detection of minor beta-thalassemia and prevention of major beta-thalassemia in the isle of Menorca. 10-year experience. *Medicina Clinica Barcelona* 1998; 110(10): 361-4.
16. Altay C, Yilgor E, Beksac S and Gurgey A. Premarital screening of haemoglobinopathies: A pilot study in Turkey. 1996; 46: 112-4.
17. Angastiniotis MA, Hadjiminis MG. Prevention of thalassemia in Cyprus. *Lancet* 1981; 1: 369-71.
18. Control of hereditary diseases. WHO technical report series 865. Geneva: 1996.
19. Cao AM, Rosatelli C, Galanello R. Control of β thalassaemia by carrier screening, genetic counselling and prenatal diagnosis: the Sardinian experience. In: Variation in the human genome. Ciba Foundation Symposium. Chichester: Wiley; 1996; 197: 137-55.
20. Ellepola SB, Beaven GH, Gunasekera LS, Arulanandan P. Hb E thalassemia in Sri Lanka: Birth Defects. Original Article Series. 1988; 23: 361-4.
21. Lucas GN, Jayawardena DR. A case of homozygous sickle cell disease in Sri Lanka. *Ceylon Medical Journal* 1991; 36(4): 172-4.
22. Gunasekara D, Perera DMD, Petrou M. Hereditary haemoglobin disorders in City dwelling Sri Lankan children, (Abstract) Proceedings of the Sri Lanka College of Paediatricians, 3rd Annual Scientific Congress. 1999: FP22.
23. Accessible publishing of genetic information. web site: <http://www.chime.ucl.ac.uk/APOGI/menu.htm>.
24. Valeketeya C, De Silva PS. Importance of genetic analysis in thalassaemia. (Abstract). Proceedings of the Sri Lanka College of Paediatricians, 3rd Annual Scientific Congress, 1999: FP23.
25. Tassiopoulos T, Stamatelos G, Zakopoulos N, Fessas P, Eliopoulos G.d. Low incidence of acute myocardial infarction in beta-thalassaemia trait carriers. *Haematologia Budapest* 1995; 26(4): 199-203.
26. Hill AV. Molecular epidemiology of the thalassaemias (including haemoglobin E). *Baillieres-Clinics in Haematology* 1992; 5: 209-38.
27. Karetti M, Ferguson M, Yardumian A, Modell B. Informing carriers of beta thalassaemia: giving the good news too. (Abstract). The 7th International Conference on Thalassemia and the Haemoglobinopathies, Bangkok, Thailand, 1999: S901.
28. Henn W. Ethical aspects of premarital genetic screening. *Human Heredity* 1996; 46: 342.
29. Perera DJB, Prematilleke MN, Withana RJ: eds. Thalassemia. Sri Lanka College of Haematologists Publication Series 1998; 1: 1-11.
30. Joint centre for sickle cell and thalassaemia disorders. Web site: <http://www-rics.bwh.harvard.edu/sickle/index.html>.
31. The Wellcome Trust, UK. International Health website: <http://www.wellcome.ac.uk/en/1/int.html>.
32. National Institutes of Health (NIH). Bethesda, Maryland 20892, USA.