Thalassaemia in Bombay: the role of medical genetics in developing countries

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This study of 200 families with thalassaemic children in Bombay showed that these children's treatment and needs place a significant, unavoidable and increasing demand on the public health services. At the same time, owing to the potentially large number of patients and the difficulties of long-term management, the situation is characterized by evasion of the problem, failure of planning, no provisions for prevention, and inadequate treatment leading to premature death among the affected children. The burden on such families is greater in developing than in developed countries because, besides caring for the chronically sick child, their lives are dominated by the high costs of treatment, often amounting to 20–30% of the income for many families. Seven mothers with no healthy children and 27 with only one healthy child had been sterilized; 90% of reproductive-age couples felt that prenatal diagnosis was a necessity. Also, ignorance and prejudice in the community led to social isolation for forty families.

The experience in Europe shows that improved treatment is the key step in controlling thalassaemia. A well-organized day-transfusion service is cost-effective, soon restoring the chidren to health and leading to increased optimism. The formation of associations by parents could mobilize community support for improved treatment and prevention, and increase public awareness of the problem. Thus cost-effective management and prevention through screening, genetic counselling, and prenatal diagnosis are at least as important in the developing as in developed countries.

Introduction

As a result of improvements in health care, infants with congenital and hereditary disorders are now often saved from death in infancy, and require long-term support. In many developing countries the haemoglobinopathies are the first major genetic problem to emerge, but the strong belief that there are higher priorities than medical genetics has been impeding the evolution of an appropriate approach. We therefore investigated the impact of thalassaemia on families in India, to see whether this neglect of inherited diseases can be justified on the grounds of limited resources.

Thalassaemia is common in the Bombay area and neighbouring state of Gujarat, the β-thalassaemia trait being carried by 1–17% in different population groups (*1*). When, for example, two trait carriers marry, there is a 1 in 4 risk in each pregnancy that the offspring will suffer from β-thalassaemia major. It is estimated that about 7000 thalassaemic infants are born annually in India, most of them, in the absence of diagnosis and treatment, dying from anaemia or infections before the age of 3 years.[a] Basic management (*2*) consists in regular blood transfusions to maintain a mean Hb level of about 12 g/dl (7.4 mmol/l); nightly subcutaneous infusions of the iron-chelating agent desferrioxamine (Desferal) are also needed to control the long-term toxicity of transfusional iron overload. This treatment can maintain good health in the long term, provided that other complications are avoided (*3*). In Bombay, access to diagnosis, basic hospital care and blood transfusion is generally available, but the cost of Desferal alone is about US$ 4500 (66 000 rupees) per patient per year, a sum completely beyond the reach of most families.

In the Mediterranean area, births of new thalassaemic infants are becoming rare as a result of control programmes that include both optimal patient care and prevention (by community education, carrier screening, genetic counselling, and prenatal diagnosis) (*4*, *5*). The question now is whether a similar approach is desirable, and would it be cost-effective and feasible in developing countries, including complex societies like those in India?

The present inquiry into the experiences and attitudes of 200 families with thalassaemic children

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living in Bombay shows that (1) the burden of chronic inherited disease is particularly heavy on families, for both economic and social reasons; (2) the steady increase in the number of such families calls for an efficient service; and (3) the provision of improved treatment, genetic counselling and prenatal diagnosis is cost-effective as well as desirable.

Population and method

The population of Bombay (8.24 million) includes diverse cultural and religious groups, each with a different frequency of thalassaemia (*1*). We estimate that about 100 infants with thalassaemia major are born in the city annually. Within the public health system, treatment for thalassaemics is available at four main centres, one of which also provides help from a charitable organization, and there are several parents' and patients' associations. Two hundred couples with thalassaemic children (over half those currently treated in the city) were contacted through these channels and agreed to be interviewed. A semi-structured questionnaire was administered by a paediatrician, a social worker and a sociologist.

The thalassaemic families were a selected group. They were drawn from the whole city although some groups where thalassaemia is common were over-represented. They also tended to a slightly higher educational and economic level, which was related to their ability to understand the disease and support its treatment. Nevertheless, an unmatched control group of parents of 200 acutely ill local children admitted to the B.J. Wadia Children's hospital permitted some useful comparisons.

Results

Table 1 shows the distribution of patients and controls by community, and the differential incidence of β-thalassaemia trait (*1*); it also indicates their educational level, and the footnote to Table 3 indicates their income level. Half the couples lived in joint families and half in nuclear families. They had had a total of 528 children, 252 of whom (48%) had thalassaemia major. (The deviation from 25% is because the families were selected by the fact of having a thalassaemic child). Of the healthy children 10% had died, with no difference between sexes. Of the thalassaemic children, 26% of the females and 18% of the males had died, 90% before 5 years of age, because they were either untreated or under-treated. Fifty-seven couples had no healthy child.

Table 1: **Communities from which the thalassaemic families and the "control" group were derived, and the fathers' educational level**

			Patients				"Controls"	
	Percentage incidence:		Father's community		Consanguineous marriage		father's community	
Community	β-thalassaemia trait	Consanguineous marriage	No.	% of total	No.	% of group	No.	% of total
Sindi	7–12	—	51	25	1	2	8	4
Lohana	6–17	—	17	8.5	0	0	2	1
Jain	+	—	16	8	0	0	1	0.5
Muslim	>3	26.5	15	7.5	8	53	24	12
Maratha	1	12	15[a]	7.5	3	19	73	36.5
Brahmin	+	6	15	7.5	0	0	8	4
Punjabi	3–6	+	12	6	4	36	1	0.5
Vaish	+	+	4	2	1	—	1	0.5
Kho/Aga	+	13	4	2	1	—	1	0.5
Christian	+	7	2	1	1	—	4	2
Bengali	3.7	—	1	0.5	0	0	1	0.5
Scheduled castes[b]	+	11	34[a]	17	7	20	51	25
Others[b]	+	+	14[a]	7	2	—	25	12.5

Educational level of father:	Patients	Controls
Less than secondary education	16%	34%
Secondary education	46%	53%
More than secondary education	39%	12%

[a] Indicates 1 inter-caste marriage; total = 3.
[b] Includes numerous groups.

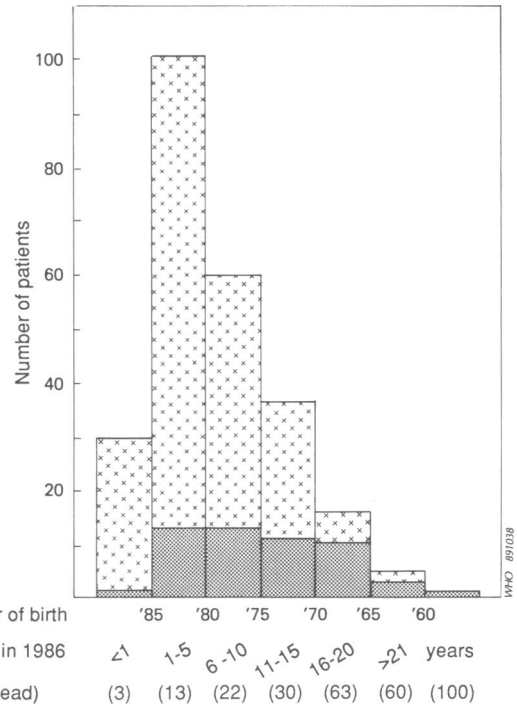
The patients' age distribution (Fig. 1) shows that the number of treated patients was rapidly increasing, and relatively few had reached the age (11 plus) when pathological effects of iron overload appear (*3*). The figure also shows that, within the same group of families, the proportion of children treated regularly and so surviving rose from 3% to 84% in the past 20 years.

Treatment

Table 2 shows the treatment provided in the four centres. Basic hospital care was free of charge, and families could obtain a cheap travel pass, but often had to find their own blood donors, and pay for preparing the blood, and for blood transfusion equipment and drugs. Where treatment was within the general paediatric service each transfusion took several days, but two centres provided a day-transfusion service. Transfusion may be complicated by difficulties in obtaining regular supplies of blood, and febrile reactions due to leukocyte antibodies occurred regularly in 22% of patients. Such difficulties led some parents to stop treatment at an early stage. Table 2 shows that these problems were least common in the centres that organized the blood supply themselves.

The mean Hb maintained by transfusion (9–10 g/dl), being less than the recommended level of 11–12 g/dl (*2*), did not completely prevent the stunted growth, distended abdomen, abnormal facial appearance, and dark pigmentation which classically distinguish thalassaemic children from their peers (*3*). It also led to frequent illnesses that interrupted schooling, and the educational level among thalassaemic children was lower than in the controls. Emotional disturbances, often noted by the parents, are more likely to be related to inadequate treatment than directly to psychological factors. Forty-two older children expressed feelings of inferiority for the above reasons.

Fig. 1. **Distribution of thalassaemic children born to families in the study, by year of birth. The hatched area represents those deceased prior to the study.**



The figure shows (*a*) the number of thalassaemic children being treated is steadily increasing; (*b*) since those now dead nearly all died before 5 years of age, the proportion of thalassaemic children surviving on long-term treatment is increasing; and (*c*) even if the number presenting annually remains unchanged, if all survive to 25 years of age (which is a reasonable estimate), the number of thalassaemic patients on treatment will at least double in the next 20 years.

Table 2: **Treatment provided in the four centres in the study**

Treatment centre	No. of families studied	Transfusion scheme: Interval (weeks)	Haemoglobin (g/dl): Before	After	Mean	Blood provided?	No. of patients with: Frequent transfusion reactions	Irregular treatment
B.J. Wadia Children's Hospital	75	4	7	11	9	No	24(32)[a]	14(19)
Tata Blood Bank (J.J. Hospital)	41	4	8	12	10	Yes	8(20)	—
St George's Hospital	38	4	7	11	9	Yes	1(3)	3(3)
Haffkin's Hospital (Blood Bank)	33	4	7	11	9	No	8(24)	—

[a] Figures in parentheses are percentages.

Table 3: **Approximate cost of each of 12 transfusions/year in the four treatment centres**

Treatment centre	Average stay (days)	Cost to hospital (Rs 65/day)	Cost to family[a] (in rupees)					Total cost/year (in rupees) to:	
			Blood[b] (350 ml)	Transfusion equipment	Desferrioxamine	Travel, food, etc.	Donation to centre	Hospital	Family
B.J. Wadia Children's Hospital	2–3	163	125	20–10	0	100–150	0	1950	2940–3780
Tata Blood Band (J.J. Hospital)	0.5	33	0	0	0[c]	50	25–80	390	900–1560
St George's Hospital	0.5	33	0–90	0–50	500 mg/wk free	25[d]	According to means	390	1440
Haffkin's Hospital (Blood Bank)	0.5	33	25–75	20–40	0	50	0	390	1140–1980

[a] Annual income of the families ranged from 6000 to over 36 000 rupees (mode = Rs 20 000 approx.); annual income of most control families was less than 20 000 rupees.
[b] Cost of blood was the cost of preparation, excluding any payment made by the family to donors.
[c] Four families at this centre bought desferrioxamine for their child.
[d] Half-rate travel concessions were negotiated by the social worker for families attending this centre.

Most families were well informed about the inherited nature of the disease, the continuing need for maintenance blood transfusions, and the risk of recurrence in further pregnancies. However, less than half the couples had been told about iron chelation therapy, because most could not afford it. Of the 22 children receiving desferrioxamine, 15 were on a quite inadequate dose.

Table 3 shows the approximate cost of this treatment to the families, and to the medical service. Transfusion alone accounted for 20–30% of the income for most families and 80% also sought ayurvedic or homoeopathic treatments for short or long periods. Only 17 families received any financial help from relatives, friends, employers or the social services. Both public and private costs were lowest in the centres that provided a day-transfusion sevice.

The family

The diagnosis of thalassaemia major had the expected profound effects on the family (*3*, *6*): 86% of the parents complained of emotional stress, anxiety and depression, 7 mothers admitted to suicidal thoughts, and one actually committed suicide after being (mis)informed that all her subsequent children would have thalassaemia major; 58% felt that their anxiety and depression led them to neglect or overprotect their healthy children. Other important problems were difficulties in obtaining blood (60%) and cost (78%), a third of the families having to take an extra job; 26 of the 46 working mothers started work, specifically to help pay for the child's treatment.

The parents' attitudes were highly ambivalent; while a majority (57%) feared that the child would die despite all their efforts, many (78%) had confidence that medical progress would provide a solution. Some 23% were determined to provide the best possible treatment at any cost, but 19% said they would not treat an affected female child. The 22% who had already lost one or more affected children were the most despairing.

Table 4 shows that the study families used all forms of contraception more often than the controls. Thirty-six couples were no longer potentially reproductive; 20 had no plans to limit their family, but most of the rest had decided against a further pregnancy because of the risk of recurrence. Seven young women without a single healthy child, and 27 with only one healthy child had been sterilized. Of the 95 couples whose reproduction was not definitively completed, 90% said they would like a prenatal diagnosis in any subsequent pregnancy (Table 5), and most would terminate an affected pregnancy. Only 10 couples would consider adoption.

Table 4: **Family planning methods used by the thalassaemic families and the control group**

	Thalassaemic families[a]		Control families	
Method	No.	% of total	No.	% of total
None	20	10	107	53
Male sterilization	7	3.5	3	1.5
Female sterilization	66	33	47	24
Condom	50	25	22	11
Pill	47	24	2	1
Abstinence	35	17	1	0.5
IUCD[b]	0	0	18	9
Total	225	100	200	100

[a] 25 families with thalassaemic children used more than one method.
[b] Intra-uterine contraceptive device.

Table 5: **Attitudes of the parents of thalassaemic children to prenatal diagnosis**

	Number	% of couples where applicable
Would like to use prenatal diagnosis	87	92
Would not use prenatal diagnosis	8	8
Not applicable[a]	105	—
Total	200	100

[a] Past child-bearing age, or divorced, or one partner sterilized or dead.

Society

Hereditary disease can be a social stigma, branding a family as unlucky and making their presence unwelcome on auspicious occasions in Indian social life. Forty families (20%) had experienced an unfavourable reaction from friends and relatives, which led to social isolation. In a few cases, healthy children were even forbidden to play with the thalassaemic child for fear they would catch the disease. Understandably some parents tried to conceal the disorder to avoid the social consequences, and to preserve the marriage chances of their healthy children. Social isolation was not influenced by whether the couple lived in a joint or nuclear family.

Discussion

Families of children with an inherited disease today face considerably greater difficulties in India than in the more developed countries. Besides emotional

problems, they are certain to be troubled by the high cost of treatment, the fear of a recurrence, and the surrounding ignorance and prejudice which often lead to social isolation. In such situations, prenatal diagnosis is therefore of even greater value than in the developed countries.

Because of its prevalence, thalassaemia provides a convenient model for working out an approach to the control of inherited disease in developing countries. The present situation in India with respect to thalassaemia closely resembles that in Europe some 25 years ago. The potentially large number of patients and the difficulties in long-term management easily lead to medical ambivalence, fatalism, and evasion of the problem. The result is failure of planning, inadequate treatment leading to chronic ill-health and premature death among the affected children, and no measures for prevention. The 20 new patients who start treatment at the study centres annually, which probably represent only a fraction of the true number, will double in the near future because of improved survival. The results of this improved treatment are already increasing the parents' optimism and also encouraging them to form associations to help increase the level of information in the community and to enlist community support for forward planning of treatment and prevention. All this has been confirmed by the experience in Europe where the recommended high transfusion scheme produced healthy children and the formation of support associations mobilized community support and improved public awareness, which enhanced the demand for prevention. Success in prevention reinforces the cycle, and the problem can gradually be brought under control (*7*).

In India, significant resources are now rather inefficiently deployed in managing the disease; at the most only 20% more blood and the same number of hospital admissions would be needed to raise the patients' mean Hb to the recommended level (12 g/dl) (*2*). An efficient service requires organization, and Table 3 shows that employing a social worker to arrange day-transfusions and blood donors, follow up the families, and help solve travel problems, etc. can actually reduce the per capita cost of treatment by 40%.

The unavailability of Desferal seems a major problem. However, present iron-chelation therapy is far from ideal. In Europe, non-compliance with treatment is now the main cause of death among young thalassaemic adults (*8*). The Indian patients are young, and complications of iron overload will take years to develop. Hope for the future in both Europe and India revolves around the development of a cheap oral iron-chelating agent to replace desferrioxamine (*9*).

The destructive effect of the disease on the family is underlined by the fact that so many mothers have been sterilized after the birth of a thalassaemic child. British Cypriots behaved in the same way before prenatal diagnosis was available (*10*), and like them the Indian parents believe prenatal diagnosis to be a necessity. Steps are now being taken to establish a competent prenatal diagnostic service available to all. Carrier detection, which is cheap and simple, is already well established in Bombay. Once the methods for prenatal diagnosis are available, it will be necessary to organize a strategy for identifying the couples at risk.

Clearly screening and genetic counselling should be available in order to avoid the first affected birth, but the social effects described here would operate against premarital testing in India at present. The planned approach is to contact the communities at particularly high risk, improve their level of information about thalassaemia, promote screening for newly-weds and in the antenatal clinics, and provide testing for those actively seeking it. Since public expenditure on chronic diseases such as thalassaemia is already considerable in Bombay and some other Indian cities, a prevention programme based on these methods would save public as well as family resources.

Though all health problems are more burdensome when resources for treatment and prevention are slender, medical genetics should have a place in health care planning in developing countries.

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Résumé

Thalassémie à Bombay: rôle de la génétique médicale dans les pays en développement

On s'imagine souvent que la génétique médicale ne présente qu'un intérêt limité dans les pays en développement. La présente étude sur 200 familles d'enfants thalassémiques à Bombay montre que le traitement et les besoins de ces enfants font peser

une charge importante, inévitable et de plus croissante sur les services de santé publique. En même temps, étant donné le nombre élevé de sujets que cette maladie peut toucher et la difficulté de sa prise en charge au long cours, la situation se caractérise par l'ignorance du problème, l'absence de planification et de prévention, et l'insuffisance du traitement, conduisant à des décès prématurés parmi les enfants atteints. La charge que représente un enfant thalassémique pour ces familles est plus grande dans les pays en développement que dans les pays développés car, en plus des soins que nécessite un enfant atteint d'une maladie chronique, ces familles doivent supporter le coût élevé du traitement, qui s'élève souvent à 20–30% de leurs revenus. Cet était de fait a conduit sept mères n'ayant aucun enfant en bonne santé et 27 autres n'ayant qu'un seul enfant en bonne santé à se faire stériliser; 90% des couples en âge de procréer estiment que le diagnostic prénatal est une nécessité. De plus, l'ignorance et les préjugés ont conduit, pour 40 de ces familles, à un rejet social.

En Europe, l'expérience montre que l'amélioration du traitement est la pierre angulaire de la lutte contre la thalassémie. Un service de transfusion bien organisé fonctionnant en hôpital de jour est rentable, car il permet d'améliorer rapidement la santé des enfants, avec un bénéfice psychologique certain. Grâce à la création d'associations de parents de malades, il est possible de mobiliser le soutien de la communauté en vue d'une amélioration du traitement et de la prévention, et également d'une meilleure sensibilisation du public à ce problème. Les succès de la prévention renforcent ce processus et petit à petit il devient possible de maîtriser la situation. A Bombay, on assiste actuellement à la mise en place d'une meilleure prise en charge et à la création de services de diagnostic prénatal.

Cette étude montre qu'une gestion efficace, associée à la prévention par le dépistage, le conseil génétique et le diagnostic prénatal, est au moins aussi importante dans les pays en développement que dans les pays développés.

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