

Psychosocial and clinical burden of thalassaemia intermedia and its implications for prenatal diagnosis

Siret Ratip, David Skuse, John Porter, Beatrix Wonke, Anne Yardumian, Bernadette Modell

Abstract

Twenty eight patients with thalassaemia intermedia and their parents were interviewed using specifically designed questionnaires to evaluate psychosocial burden. Hospital notes were analysed for clinical burden.

A wide variation was found for both patients and parents, ranging from virtually unaffected to severely affected. Normal sexual function and setting up a family were mentioned by patients and parents as being particularly important for quality of life. Over half (58%) of the patients had problems with sexual maturation and functioning, and continuous monitoring of all patients with thalassaemia intermedia by a paediatric endocrinologist is therefore strongly indicated.

Most parents said, in light of their experiences, that they would opt for prenatal diagnosis and termination of affected pregnancies even if a genotype predicting the mild form of disorder were discovered.

(*Arch Dis Child* 1995; 72: 408-412)

Keywords: thalassaemia intermedia, psychosocial, clinical, prenatal diagnosis.

The homozygous state for β thalassaemia usually results in thalassaemia major, which requires monthly transfusions and regular infusions for life of the iron chelating agent desferrioxamine. Some patients are less severely affected and survive either with no blood transfusions or without regular blood transfusion. This milder syndrome is termed thalassaemia intermedia.^{1 2} Its relative frequency in different populations ranges from about 2-10% of cases.¹ Prenatal diagnosis of homozygous β thalassaemia, with the choice of selective abortion of affected fetuses, is now accepted practice. Hitherto it has not been possible to discriminate between fetuses with thalassaemia major and intermedia. This is a source of discomfort for clinicians as some terminations result in the loss of fetuses who would have developed into mildly affected children.³

A significant amount of information is now available on the genetic basis of thalassaemia intermedia. Important ameliorating genetic factors are mild β thalassaemia mutations,⁴⁻⁷ coinheritance of α thalassaemia,^{8 9} and presence of polymorphisms adjacent to the β globin gene complex that enhance gammaglobin chain

production.^{10 11} However, the precise relationship between each genotype and phenotype is not yet established. Even when it becomes possible to predict phenotype accurately from genotype, it will be necessary to know the spectrum of psychosocial burden of thalassaemia intermedia in order to inform prospective parents, who must decide whether or not to keep a pregnancy with a predicted 'mild' genotype. If the severity of the intermedia phenotype correlates predictably with psychosocial burden, then parents with fetuses with a milder genotype may choose to continue with the pregnancy. On the other hand, if an intermedia phenotype is always associated with adverse psychosocial consequences then parents may choose not to continue such a pregnancy. To date there have been no studies of the psychosocial burden for the patients and their parents. We therefore undertook this study of the clinical and psychosocial aspects of thalassaemia intermedia.

Patients and methods

PATIENTS

The study was undertaken at University College, Whittington, and North Middlesex Hospitals; we recruited 28 patients with thalassaemia intermedia and their parents. Criteria for inclusion were: patients with two β thalassaemia genes who had not been transfused at all, were not regularly transfused, or were not regularly transfused until after the age of 6 years.

We informed patients and their parents of the study by post, and sought their consent. Those who did not respond were contacted by telephone. Nearly all (27/28) patients and most (17/22) parental pairs participated in the study. Some parents were not interviewed for a variety of reasons, including residence abroad, death, and refusal by patients to allow parents to be contacted.

The patients were aged 5 to 66 years (mean (SD) 24 (9) years): two pairs of cases were siblings; 23/28 were over 16 years of age; 12 were male and 16 female. Seventy per cent were born in the UK. Seven were married, one separated, one divorced, one widowed, and 13 were single. Six patients had a total of 10 children. Most parents (70%) were of Mediterranean descent, mainly Cypriots. Ethnic origin of the subjects is shown in table 1.

METHODS

Psychosocial burden

Patients aged 16 years and over, and all

University College
London Medical
School, Department of
Haematology
S Ratip
J Porter

Department of
Obstetrics and
Gynaecology
B Modell

Department of
Psychological
Medicine, Institute of
Child Health, London
D Skuse

Department of
Haematology,
Whittington Hospital,
London
B Wonke

Department of
Haematology, North
Middlesex Hospital,
London
A Yardumian

Correspondence and reprint
requests to: Dr S Ratip,
Department of Haematology,
University College Hospital,
A and E Building, Grafton
Way, London WC1E 6AU.

Accepted 8 February 1995

Table 1 Ethnic origin of patients

	Patients	Parents
Greek Cypriot	11	17
Turkish Cypriot	8	16
Indian	2	4
Iranian	2	4
Afro-Caribbean	2	3
African	1	2
Kurdish	1	2
Italian	1	2

parents, were interviewed either in the clinic or at home depending on their choice. Pre-existing questionnaire measures of psychosocial adjustment were found either to be inappropriate for this chronic inherited disease or too cumbersome for use in a clinical setting.¹²⁻¹⁶ We therefore designed a new instrument, in the form of a structured interview, for measuring the potential psychosocial burden of thalassaemia intermedia. The questions were designed to be simple, non-judgmental, and acceptable to all cultures. The main topics included are given in the results section. Three versions were developed complete with operational definitions about precisely what was meant by each of the degrees of severity coded: (A) for adult patients; (B) for parents to answer about themselves; and (C) for parents to answer about patients under 16 years of age. The interview lasted approximately one hour per person (range 45 minutes-1.5 hours). At the end of the interview each response was graded 0-3 corresponding to the degree of impairment (0=unaffected, 1=mild, 2=moderate, 3=severe). We ensured reliability of grading by consensual rating of a proportion of interviews (SR/DS) and employed standard parametric and non-parametric statistical procedures, the data being analysed by the SPSS for Windows statistical package.

Clinical burden

Clinical information collected from the notes of consenting patients included present clinical status, a short medical history (age and circumstances of diagnosis, haemoglobin concentration at presentation and before and after splenectomy, transfusion history, desferrioxamine treatment history), and a checklist of clinical problems specifically associated with thalassaemia intermedia. During the interview with the patient the family tree was completed, demographic data obtained, and the clinical history checked. Medical records were examined for all patients, and all data required for scoring the clinical and psychosocial burden were identified. Where necessary, the relevant consultant was contacted to clarify clinical issues. In addition, all patients were studied by DNA methods for the genetic ameliorating factors listed in the introduction. The latter results will be published separately.

Results

PSYCHOSOCIAL DATA

(A) Psychosocial burden for adult patients

The range of symptoms reported covered virtually the whole spectrum of psychosocial

burden, from hardly affected at all to severely affected. Nearly half (48%) of the total responses were in the 'unaffected' category. There were unaffected patients for each of the categories of psychosocial burden.

Education was affected in 43% of the patients, mostly as a result of having to take time off school due to thalassaemia intermedia. Just over half (57%) had had to take time off school because of their illness. Periods of absence varied from one day or less, to more than one week per month. The majority of the affected patients complained that they had done less well academically than they thought they were capable of doing, and they attributed their relative failure to their thalassaemia intermedia.

Sports activity was affected in 62% of the patients, who complained of tiredness and sub-optimal performance due to thalassaemia intermedia. One third (33%) could not participate in sports at all due to symptoms such as weakness or dyspnoea, or occasionally on medical advice.

Two thirds (67%) felt a degree of stigmatisation ranging from being called 'a yellow face' at school, to relationships being broken, or being unemployed because of thalassaemia intermedia. A similar proportion (62%) expressed some degree of feeling different from their peers and siblings. Their reasons included physical factors such as weakness and bone pains and social factors such as inability to have a family.

More than one half (57%) had a degree of anxiety, ranging from worrying about thalassaemia intermedia sometimes to worrying about it all the time. Examples of worries were fear of early death, not being able to set up a family, or having to start transfusions and desferrioxamine treatment.

In 28% of patients, social activities were reduced to a severe degree. A major reason in these patients was the need, on at least five nights out of seven, to take subcutaneous desferrioxamine infusions for iron chelation, a procedure which takes up to 10 hours each time. Occasionally, other factors had a role, such as leg ulcers. As a result relationships with friends were affected adversely; 14% of the patients were virtually housebound. A substantial minority (19%) frequently referred to thalassaemia intermedia as a significant obstacle to living a normal life and it made them feel defective or dependent. A similar proportion (19%) had problems with social integration in that they were either unemployed or unable to set up a family as a result of thalassaemia intermedia. One in four (24%) had told no-one except their best friends about their illness. Reasons given varied from 'none of their business' to 'they will think that I have AIDS if they know that I was transfused'.

(B) Psychosocial burden for parents

Four out of five (81%) parents would have chosen prenatal diagnosis if it had been available to them before their affected child was

Table 2 Clinical description of patients

Patient No	Data at presentation				Data at present (mean values over the last 12 months)					
	Age (years)	Haemoglobin (g/l)	Fetal haemoglobin		Age (years)	No of transfusions	Mean haemoglobin (g/l)	Spleen (cm) or age at splenectomy (y)	Desferrioxamine (mg/kg/day)	Ferritin (μ g/l)
1	Birth	114	98	112	5	0	63	7 cm	0	48
2	1	-	99	-	9	3	96	3 cm	37	2125
3	2.5	80	35.6	28	15	8	107	10 y	21	1265
4	0.8	87	45	39	14	6	106	9 y	29	1383
5	1.5	77	97	75	8	9	100	7 y	0	557
6	5.5	86	87	75	21	0	83	6.5 y	0	200
7	3.5	86	66	57	22	4	92	9 y	19	1442
8	19	-	98	-	32	0	117	12 cm	0	211
9	3.5	-	-	-	23	0	51	7 y	0	520
10	3	-	-	-	19	2	78	7 y	0	924
11	9	66	-	-	28	4	70	12 y	20	9125
12	5	-	-	-	27	12	102	9 y	12	1744
13	5	46	74	34	25	1	95	10 y	32	785
14	3	-	-	-	29	4	87	8 y	40	3295
15	5	94	97.8	92	28	0	84	15 y	0	555
16	4	-	-	-	32	3	83	16 y	0	345
17	4	-	-	-	25	0	80	21 y	0	200
18	-	-	26	-	38	1	67	11 y	18	1222
19	3	50	41	21	39	10	82	6 cm	28	885
20	1.8	104	42	44	26	0	78	8 y	0	1265
21	54	80	11.5	09	66	17	122	55 y	32	1650
22	0.3	47	75	35	39	0	76	25 y	0	740
23	3.5	95	96.5	92	18	0	100	5 y	0	360
24	8	85	80	68	28	1	82	20 y	23	1853
25	1.5	69	98.4	68	18	0	89	8 y	0	3675
26	13	-	69.3	55	24	1	78	13 y	0	671
27	1	80	68	64	19	0	94	5 y	0	751
28	19	-	59	75	35	0	127	0 cm	0	59

born, and with hindsight said they would have chosen to terminate every affected pregnancy. Only 3/25 couples would either definitely have chosen to continue or would have considered continuing a pregnancy if they had known the fetus had thalassaemia intermedia. One of these couples was of African origin, in another the father was Afro-Caribbean and the mother Cypriot, and the third were Cypriots with the lowest psychosocial scores in the sample for both parents and children. One in four (25%) of the couples would have had more children if they had not had a child with thalassaemia intermedia.

Reported symptoms covered most aspects of the psychosocial burden spectrum for which we inquired. The great majority (88%) of parents suffered from anxiety, ranging from sometimes worrying about thalassaemia intermedia to worrying a lot or all of the time. Principal sources of anxiety included fear of death or suffering for their child, and whether he/she would ever be able to set up a family. About a quarter (26%) of parents had some degree of confusion about

thalassaemia intermedia. Some had wrong beliefs, for example two couples felt that marrying their cousin was the entire reason for having an affected child. Two couples knew nothing about thalassaemia intermedia at all.

Social isolation was present in 51% of the parents. This ranged from needing more support at times, to having no one to turn to when in need of support. One quarter (25%) were either unable to work or in financial hardship due to thalassaemia intermedia. Reasons included having to take time off work or take part time work because the child needed frequent hospital visits, and not being able to concentrate on work due to worrying. Employment was unaffected in 69% of parents.

(C) Psychosocial burden for patients under 16 years of age

The number of patients in this group (five) is too small to make any general comments about psychosocial burden in children affected with thalassaemia intermedia. However, three had problems with time off school, and according to their parents four were different from their friends/siblings. Reasons included physical factors such as being weaker, or not appearing to enjoy life as others.

CLINICAL DATA

Age at diagnosis varied from birth to 19 years, though one exceptional patient presented at 54 years complaining of lethargy. The mean haemoglobin concentration of the untransfused patients was 86 g/l (range 51–117 g/l). The ferritin concentration was raised in all but two patients with values over 1000 μ g/l in 12/28 of the patients, of whom 10 were on desferrioxamine (see table 2).

One third (31%) of patients were not being transfused, and 69% were regularly transfused

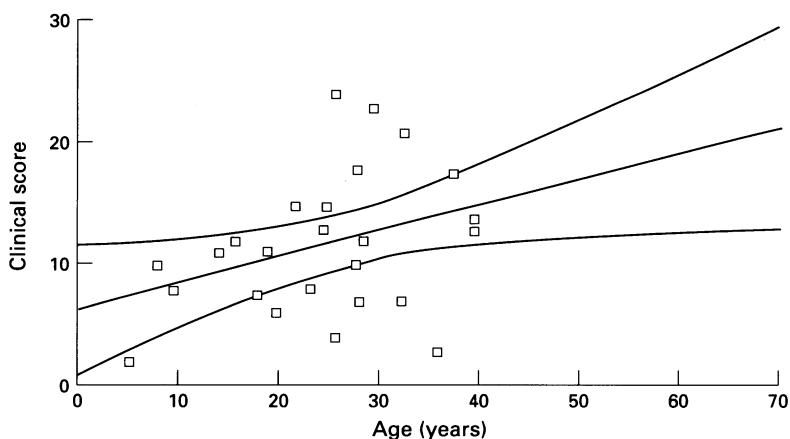


Figure 1 Relationship of patient clinical scores and age; $r=0.54$ (95% CI 0.18 to 0.77).

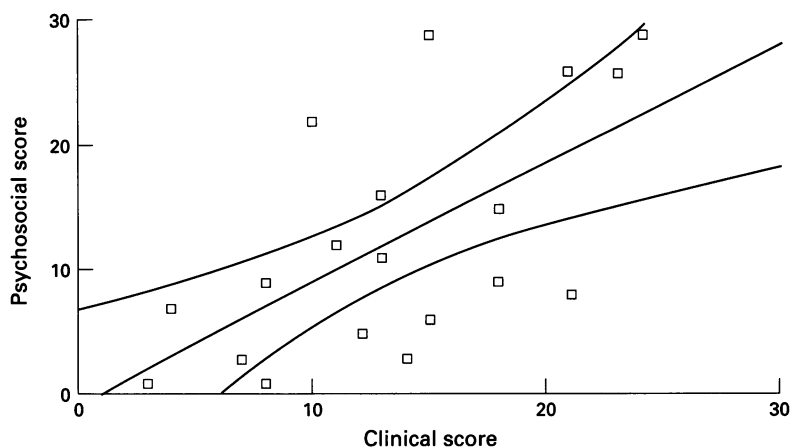


Figure 2 Relationship of psychosocial and clinical data for adult patients; $r=0.69$ (95% CI 0.35 to 0.87).

at intervals of 3–12 months. As a consequence of thalassaemia intermedia, 23/28 (81%) had undergone splenectomy at ages 5 to 25, and 31% had undergone cholecystectomy. One in four (23%) had suffered leg ulcers and most of these had more than two episodes of ulceration which had lasted more than two years. Over half (58%) had experienced some degree of sexual dysfunction, with symptoms that ranged from delayed puberty and infertility to impotence and early menopause. Mobility was affected in 42% ranging from weakness on walking leading to intermittent rest, to being able to walk less than half a mile or climb less than 10 stairs. Half (51%) of the patients had some degree of facial deformity, which was moderate or severe in 20%. Moderate or severe bone and/or joint pain, interfering with daily activities, was noted in 20% of the patients and 15% had sustained more than two pathological fractures. A minority (12%) of the patients had been admitted to hospital overnight more than twice a year.

INTERRELATION OF PSYCHOSOCIAL AND CLINICAL DATA

The relationships are presented in figs 1–3. Figure 1 presents the relationship between clinical burden scores and patients' age. There is evidence that clinical burden increases as the

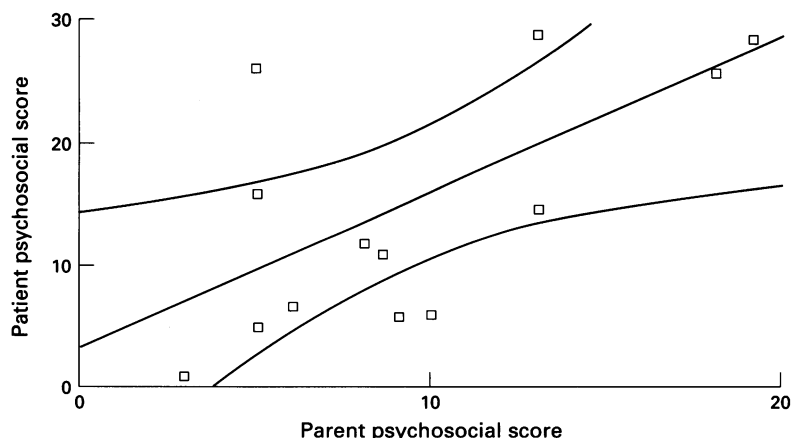


Figure 3 Relationship of parent and patient psychosocial data; $r=0.69$ (95% CI 0.16 to 0.91).

patient gets older. This is supported by a positive correlation overall of 0.54, with a 95% confidence interval (CI) of 0.18 to 0.77. Figure 2 presents the relationship between the adult patients' psychosocial burden and their clinical burden scores. The hypothesis that a high clinical burden would be associated with a high psychosocial is supported by a positive correlation between these variables of 0.69 (95% CI 0.35 to 0.87). Figure 3 presents the relationship between adult patients' psychosocial burden and their parents' psychosocial scores. We found a large positive correlation of 0.69 (95% CI 0.16 to 0.91).

The hypothesis that parents' psychosocial score would be determined primarily by the clinical burden of thalassaemia intermedia for their child was not supported by the study. The correlation was only 0.23 (95% CI -0.41 to 0.56).

Discussion

The category 'thalassaemia intermedia' includes all patients with homozygous β thalassaemia who are not transfusion dependent, and is known to cover a wide range of clinical severity. This study presents a quantitative analysis of the frequency of the physical and psychosocial problems associated with thalassaemia intermedia in a group of families resident in London. The sample includes all cases of thalassaemia intermedia attending three north London hospitals with the largest number of thalassaemia patients, and is therefore representative.

It is remarkable that only 5/28 patients are under 16 years of age. There are two possibilities that may explain this. Firstly, prenatal diagnosis has led to a great decrease in births of children with homozygous β thalassaemia of all types. Secondly, some thalassaemia intermedia patients, especially those more recently diagnosed, may have been inappropriately treated as thalassaemia major with regular blood transfusions masking their own haemoglobin concentration which may be acceptable without support.

The study shows that there are thalassaemia intermedia patients at the mild and severe ends of the spectra of clinical and psychosocial burdens. It also shows that there are mildly and severely affected parents. We believe, therefore, that the questionnaires developed for this study may be a convenient instrument for identifying patient and parents who need additional clinical care and psychological support.

Our most important finding was that 88% of the parents worried about thalassaemia intermedia sometimes, a lot, or all the time. This is particularly remarkable considering that most of the patients are adults. This high level of anxiety probably accounts for the fact that 81% of the parents (70% of Mediterranean descent, mainly Cypriots) would choose prenatal diagnosis, and would terminate every affected pregnancy. The implication is that, in this ethnic group, even if mild genotypes leading to mild phenotypes and a low psychosocial burden are demonstrated prenatally,

parents are likely to opt for termination of pregnancy. This conclusion cannot be generalised, as decisions might be different in other ethnic groups such as Africans or Afro-Caribbeans. In addition, uptake of prenatal diagnosis for sickle cell disease is lower among Afro-Caribbeans than among Africans.¹⁷ The influence of ethnic/cultural differences needs to be studied further.

The number of patients in the under 16 age group was too small to make any general comments.

More than half (58%) of the patients had sexual dysfunction. Worrying about problems with setting up a family also featured frequently as a major cause of anxiety for both patients and parents, and was an important reason for patients feeling different, having a poor self image, and having difficulties with social integration. Developing and maintaining normal sexual functioning is clearly a major determinant of quality of life for patients and their parents. We recommend all thalassaemia intermedia patients are monitored by a reproductive endocrinologist, who can work as part of the thalassaemia care team.

The study provides some tentative answers to important questions such as: How does the clinical burden for the patient affect the psychosocial burden for patient and parents? Is there a relationship between the psychosocial burden for patient and parents? To what extent are the clinical and psychosocial burdens related to the patient's age?

The suggestions that a high clinical burden is associated with a high psychosocial burden for the patient, and that a high psychosocial burden for the patient correlates with a high psychosocial burden for the parents, are supported. There are exceptions to these relationships, and the psychosocial burden felt by the parents is influenced by their attitude towards the illness, which in turn is probably determined by cultural and personal influences. Therefore, every case should be considered individually. No significant correlation was found between patients' clinical burden and parental psychosocial burden. Therefore, it is not the clinical burden, but the psychological burden, that determines the most significant impact on the family. This is important information for genetic counsellors.

The study also provides evidence that clinical burden increases as the patient gets older. This is because problems such as sexual dysfunction, osteoporosis and leg ulcers occur later on, and also the treatment of some of these problems is by regular blood transfusion which in turn necessitates the use of desferrioxamine. This observation is also important for genetic counselling.

On the basis of this study, the high proportion of parents who would opt for prenatal diagnosis and termination of affected pregnancies, and the observed extent of psychosocial burden affecting the patients and the parents, justifies the offer of prenatal diagnosis to parents who are likely to have children with thalassaemia intermedia. It is important to note, firstly, that the attitudes and psychosocial burden can differ between ethnic groups and hence the study should be extended to groups under-represented in this sample; secondly, that there will be exceptions due to differences in personal attitudes towards the illness, and, thirdly, that with scientific progress leading to improved care, the attitudes of the subjects may change.

We acknowledge the funding of Dr Siret Ratip by the European Community Commission. Professor Bernadette Modell is a Wellcome principal research fellow.

The structured interview questionnaires and checklist of problems associated with thalassaemia intermedia are available from Dr Ratip.

- 1 Modell B, Berdoukas V. *The clinical approach to thalassaemia*. London: Grune and Stratton, 1984.
- 2 Erlanson ME, Brilliant R, Smith CH. Comparison of sixty-six patients with thalassaemia major and thirteen patients with thalassaemia intermedia. *Ann NY Acad Sci* 1964; 119: 727-35.
- 3 Wainscoat JS, Thein SL, Weatherall DJ. Thalassaemia intermedia. *Blood Rev* 1987; 1: 273-9.
- 4 Wainscoat JS, Weatherall DJ, Old JM. The molecular basis for the clinical diversity of beta thalassaemia in Cypriots. *Lancet* 1983; i: 1235-8.
- 5 Di Marzo R, Dowling CE, Wong C, et al. The spectrum of beta thalassaemia mutations in Sicily. *Br J Haematol* 1988; 69: 393-7.
- 6 Antonarakis Se, Kang J, Lam VMS, et al. Molecular characterisation of beta-globin gene mutations in patients with beta thalassaemia intermedia in South China. *Br J Haematol* 1988; 70: 357-61.
- 7 Thein SL, Hesketh C, Wallace RB, et al. The molecular basis of thalassaemia major and thalassaemia intermedia in Asian Indians: application to prenatal diagnosis. *Br J Haematol* 1988; 70: 225-31.
- 8 Weatherall DJ, Pressley L, Wood WG, et al. Molecular basis for mild forms of homozygous beta thalassaemia. *Lancet* 1981; i: 527-9.
- 9 Wainscoat JS, Kanavakis E, Wood WG, et al. Thalassaemia intermedia in Cyprus: the interaction of alpha and beta thalassaemia. *Br J Haematol* 1983; 53: 411-6.
- 10 Cappellini MD, Fiorelli G, Bernini LF. Interaction between homozygous beta zero thalassaemia and the Swiss type of hereditary persistence of foetal haemoglobin. *Br J Haematol* 1981; 48: 561-72.
- 11 Thein SL, Wainscoat JS, Sampietro M, et al. Association of thalassaemia intermedia with a beta-globin gene haplotype. *Br J Haematol* 1987; 65: 367-73.
- 12 Rutter M. A children's behaviour questionnaire for completion by teachers: preliminary findings. *J Child Psychol Psychiatry* 1967; 8: 1-11.
- 13 Rutter M, Tizard J, Whitmore K. Appendix 6: a children's behaviour questionnaire for completion by parents. *Education, health and behaviour*. London: Longmans, 1970: 412-21.
- 14 Goldberg DP, Hillier VF. A scaled version of the general health questionnaire. *Psychol Med* 1979; 9: 139-45.
- 15 Deasy-Spinetta P, Spinetta JJ, Oxman JB. The relationship between learning deficits a social adaptation in children with leukaemia. *Journal of Psychosocial Oncology* 1988; 6 (3/4): 109-21.
- 16 Achenbach TM. *Manual for the child behaviour checklist: 2/3 1992 profile*. Burlington, VT: University of Vermont Department of Psychiatry, 1992.
- 17 Petrou M, Brugiattelli M, Ward RHT, et al. Factors affecting the uptake of prenatal diagnosis for sickle cell disease. *J Med Genet* 1992; 29: 820-3.