An analysis of relative costs and potential benefits of different policies for antenatal screening for β thalassaemia trait and variant haemoglobins

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Abstract

***Aims*—To investigate the costs and potential benefits of different policies for antenatal screening for haemoglobinopathies in two multiethnic London communities.**

***Methods*—1000 consecutive antenatal patient samples referred to each of two London teaching hospital laboratories for haemoglobinopathy testing were investigated using the standard procedures of the laboratory in question. When the standard procedures did not include high performance liquid chromatography (HPLC), this technique was added, in order to assess its diagnostic value and cost–effectiveness. A comparison was made between the costs and potential benefits of universal testing for variant haemoglobins and β thalassaemia trait using HPLC and the costs and potential benefits of universal testing for variant haemoglobins and selective testing for β thalassaemia trait using the mean cell haemoglobin (MCH) as a screening test and less automated techniques than HPLC for definitive diagnosis.**

***Results*—The costs of the two policies were found to be comparable, as the higher reagent/instrument costs of HPLC were offset by the lower labour costs. Universal testing of 2000 consecutive samples did not disclose any extra cases of β thalassaemia trait which would not have been detected by universal screening and selective testing. However, six patients were found to have a haemoglobin A2 variant which can interfere with the diagnosis of β thalassaemia trait.**

***Conclusions*—The introduction of universal testing by HPLC into British laboratories could be cost neutral and has potential benefits. If a higher cost is accepted then the greater degree of automation could be used to release skilled staff for other tasks within the laboratory.**

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The British Committee for Standards in Haematology (BCSH) has recently prepared a guideline for the laboratory diagnosis of disorders of globin chain synthesis.[1] This includes recommended procedures for the diagnosis of both haemoglobinopathies and α^0 and β thalassaemia trait in pregnant women. Such testing is required for the prediction of clinically significant disorders of globin chain synthesis in the fetus.

The definitive diagnosis of α^0 thalassaemia trait requires DNA analysis and in Britain this is generally carried out in a reference laboratory when red cell indices in a woman of an appropriate ethnic origin suggest this diagnosis. However, the diagnosis of β thalassaemia trait and of relevant haemoglobinopathies is usually carried out in diagnostic haematology laboratories within hospitals.

The BCSH guideline recommends that, as a minimum, all antenatal patients who are not of northern European origin be tested for the presence of variant haemoglobins and that all women, irrespective of ethnic origin, be screened for β thalassaemia trait. When the percentage of antenatal patients who are not of northern European ethnic origin exceeds 15% it is advised that testing for haemoglobinopathies be universal, as is also suggested by the report of the Standing Medical Advisory Committee on Sickle Cell, Thalassaemia and other Haemoglobinopathies (SMAC).[2] The BCSH guideline and the SMAC report recommend that screening for β thalassaemia trait be performed by assessment of the mean cell haemoglobin (MCH), with quantification of haemoglobin A2 for definitive diagnosis being performed only in women with a reduced MCH. This policy means that rare patients with β thalassaemia with normal red cell indices but a raised haemoglobin A2 would be missed.

The introduction of improved reagent/instrument systems for high performance liquid chromatography (HPLC) means that it is now feasible to perform A2 measurements on all antenatal patients, thus reducing the probability of missing cases of β thalassaemia. HPLC has the advantage that a single test permits the detection of variant haemoglobins and the quantification of haemoglobin A2. A recent audit of representative United Kingdom laboratories carried out by the UK Forum for Haemoglobin Disorders found that this policy has been introduced in a significant minority of hospitals, five of 38 surveyed.[3] Despite the introduction of such universal testing (in contrast with universal screening by red cell indices), there has been little consideration of the cost of implementing this policy or of the cost–benefit ratio of universal testing.

We therefore set out to perform an analysis of comparative costs and to assess potential benefits of two policies for antenatal screening. We measured haemoglobin A2 concentration

Table 1 Ethnic origin of patients tested expressed as a percentage

Ethnic origin	*Laboratory A*	*Laboratory B*
White northern European	42.7	
White, unspecified		55.1
Afro-Caribbean	10.4	2.8
African	8.0	3.3
Black, unspecified		1.8
Total black	18.4	7.9
Mediterranean*	5.4	
Chinese/S E Asian	3.0	0.7
Indian subcontinent ("south Asian")	7.2	4.5
Other†	10.2	5.8
Not known	13.0	26.0

*For laboratory B this group is included in the "Other" group.
†Including North African, Middle Eastern, South American, and mixed ancestry.

Table 2 Diagnoses made by application of each laboratory's standard procedures to 1000 consecutive women

Diagnosis	*Laboratory A*	*Laboratory B*
Sickle cell trait	27	28
Haemoglobin C trait	3	2
Haemoglobin E trait	5	2
Haemoglobin D Punjab trait	2	2
Sickle cell/haemoglobin C disease		1
β Thalassaemia trait	8	9
Haemoglobin A2 variant	0*	1
Other variant haemoglobin	6†	
Haemoglobin F > 2%	1‡	1

*Six patients were found to have a split A2 band by HPLC which had not been detected by standard procedures.
†Haemoglobin D-Iran trait, haemoglobin J-Baltimore trait, other haemoglobin D/G trait, not further characterised (two cases), haemoglobin Siriraj trait, haemoglobin H disease.
‡A diagnosis of hereditary persistence of fetal haemoglobin was made in this patient; a raised haemoglobin F percentage was detected in a further 15 patients by HPLC but in each case the concentration was only slightly above 2%.

and screened for variant haemoglobins by HPLC in 2000 consecutive antenatal patients, 1000 from each of two laboratories. Laboratory A was in the department of haematology at St Mary's Hospital, London, and laboratory B was in the department of haematology at Hammersmith Hospital, London. Laboratory A served antenatal patients from the hospital's two antenatal clinics. Laboratory B tested patients from Queen Charlotte's Hospital, London, as well as women from its own antenatal clinic. Investigation of patients from two laboratories meant that two groups showing a different ethnic mix could be investigated. Both hospitals had more than 15% of antenatal patients who were not white northern Europeans.

Methods

In laboratory A, blood counts were performed on a Bayer-Technicon automated analyser and other tests for routine diagnostic purposes were carried out according to the standard practice in that laboratory. Specifically, all patients, irrespective of ethnic origin, were tested for variant haemoglobins by electrophoresis on cellulose acetate at pH 8.2–8.6. Red cell indices were scrutinised and when the MCH was less than 27 pg haemoglobin A2 was quantified by microcolumn chromatography (Helena Beta-thal HbA2 Quick Column). Samples containing variant haemoglobins were further studied, as appropriate, by a sickle solubility test (Ortho Sickledex), electrophoresis on agarose gel at pH 6.0–6.2 (Helena Titan Gel Acid Hb), HPLC, and for certain rare haemoglobins, mass spectrometry (by courtesy of Dr Barbara Wild, King's College Hospital, London). A diagnosis of β thalassaemia trait was generally made when the haemoglobin A2 concentration was greater than 3.5%, a reference range of 2.2–3.5% having previously been established. Borderline results (3.5–3.6%) were repeated and, when necessary, a further sample was obtained for repeat analysis before a definitive diagnosis was made. Once all tests necessary for diagnostic purposes had been performed, the residual sample was used for measurement of haemoglobin A2 and screening for variant haemoglobins by HPLC, using a Bio-Rad variant instrument, β thal short program.

In laboratory B, blood counts were performed on a Sysmex SE9000. All samples, irrespective of red cell indices and ethnic origin, were investigated by HPLC, as above. A diagnosis of β thalassaemia was generally made when the haemoglobin A2 concentration was greater than 3.7%, a reference range of 2.2–3.3% having previously been established in this laboratory. Variant haemoglobins were further characterised by methods similar to those described above.

In both laboratories, patients who appeared to be iron deficient or to be at risk of α^0 thalassaemia trait were appropriately investigated. They have not been considered further in this study.

Ethnic origin used in the analysis was either that recorded on the patient administration system (PAS), according to the woman's own assessment of her ethnic origin, or that recorded by the antenatal clinic staff after consultation with the patient.

All costings were carried out using the costs of kits and reagents to the hospitals concerned, as of 1 June 1998. The costs of service contracts and maintenance of instruments are included in the reagent costs. Labour costs were calculated for the mid-point of the Medical Laboratory Scientific Officer 1 (MLSO 1) salary scale on this date, including the London allowance but excluding the "on-costs" to the employer, usually taken as 15%. The costs and benefits of different technologies and different policies for investigating antenatal patients were compared. The costs of clerical work (receipt of specimens and recording and issuing of results) were not included in the calculations of costs but were estimated to be similar for the two policies.

Results

The ethnic origin of the two patient groups is shown in table 1. It will be noted that laboratory A had a larger proportion of patients known to be not of northern European origin (44.3% *v* 18.9%) and that both laboratories had a large number of women whose ethnic origin was not known to the laboratory staff. In all, 20 significant abnormalities were detected in patients of unknown ethnic origin (five in laboratory A, 15 in laboratory B) and, in addition, sickle cell trait was detected in a woman who was stated to be "Caucasian," indicating that selective screening for variant haemoglobins and thalassaemic disorders cannot be carried out successfully if information on ethnic origin is incomplete or unreliable.

Table 3 Costings of two policies for testing for variant haemoglobins and β thalassaemia trait

Policy 1
Cellulose acetate electrophoresis on all patient samples, supplemented by measurement of haemoglobin A2 by microcolumn chromatography on all samples with an MCH less than 27 pg, by a sickle solubility tests on all samples with a variant haemoglobin with the mobility of haemoglobin S, and by citrate agar electrophoresis on all samples containing a variant haemoglobin other than S

	Cost of application to 1000 patients		
	Reagents	*Labour*	*Total*
Laboratory A patients	£1015	£1119	£2134
Laboratory B patients	£933	£1074	£2007

Policy 2
HPLC on all patient samples supplemented by a sickle solubility test when a haemoglobin with the characteristics of haemoglobin S was present and by cellulose acetate and citrate agar electrophoresis when any other variant haemoglobin was present

	Cost of application to 1000 patients		
	Reagents	*Labour*	*Total*
Laboratory A patients	£1747	£215	£1963
Laboratory B patients	£1747	£213	£1950

The diagnoses made by application of the laboratories' standard procedures are shown in table 2. For laboratory A patients, no cases of β thalassaemia trait were detected by HPLC which had not already been detected by performing haemoglobin A2 measurements on all women with an MCH value less than 27 pg. Similarly, all cases diagnosed by routine procedures (HPLC) in laboratory B would have been detected if selective testing of those with an MCH of less than 27 pg had been employed. A total of 228 women had an MCH of less than 27 pg, 131 from laboratory A and 97 from laboratory B. Of these 17 (7.4%) had β thalassaemia and a further 38 (16.6%) had a haemoglobinopathy. Universal measurement of haemoglobin A2 meant that measurements were performed on a further 1772 women without any further cases of β thalassaemia trait being diagnosed.

Costings of different policies applied to the two patient groups are shown in table 3. It will be noted that although reagent costs are considerably greater when universal testing by HPLC was used this was counterbalanced by the considerably lower labour costs.

Discussion

In this analysis of 2000 consecutive antenatal patients, 17 patients with β thalassaemia trait and 79 with haemoglobinopathies (73 likely to be significant for genetic counselling) were detected; this represents a total of 90 significant abnormalities (4.2% of women investigated). In addition, there were several women who required further assessment because of probable α^0 thalassaemia trait. All 90 significant abnormalities would have been detected by implementation of the recently promulgated BCSH guidelines.[1] However, it should be noted that, using its standard procedures, laboratory A missed a split A2 band in six patients. Although a split A2 band, indicative of a variant haemoglobin A2 band, is not in itself clinically significant, failure to detect it may mean that rare cases of β thalassaemia trait in women who also have a haemoglobin A2 variant may be missed.

The results of this study illustrate the importance of having access to information on ethnic origin if selective screening is to be carried out. Both our series of patients included a disappointingly large number of women in whom the ethnic origin was unknown to the laboratory. Unless information on ethnic origin is both complete and accurate, selective screening is likely to lead to an unacceptable number of abnormalities being missed; in this series, 20 of the 90 significant abnormalities detected were in women of unknown ethnic origin and would not have been detected without a policy of universal screening.

Implementation of universal testing (rather than universal screening) for β thalassaemia trait could be cost neutral for hospitals with a patient population similar to ours and with costs similar to ours. Although reagent/instrument costs of universal testing are greater, the staff costs are considerably less, so that the overall costs show little difference. However it should be noted that the costings are dependent on the prices negotiated with manufacturers for kits and reagents and these are usually dependent on annual work load.

Our results indicate that universal application of HPLC in an ethnically mixed British population would not often yield extra clinically relevant information. The policy of universal testing for variant haemoglobins and screening plus selective testing for β thalassaemia trait detects the great majority of significant abnormalities. Nevertheless, for a rare individual woman, information gained by universal testing could be very important. Although universal application of HPLC did not detect any extra cases of β thalassaemia in our series, we did detect seven patients (0.35%) with a split haemoglobin A2 band indicative of a variant haemoglobin A2. β Thalassaemia trait co-inherited with a variant haemoglobin A2 may well be missed if the standard policy is to use cellulose acetate electrophoresis and microcolumn chromatography. Universal testing also reduces the likelihood of human error leading to failure to test a woman with a low MCH.

There are no significant economic arguments either for or against implementation of universal testing by HPLC in United Kingdom hospitals with a significant proportion of patients who are not of northern European origin. However, it is unlikely in practice that the adoption of such a policy would be cost neutral. Because most British hospitals currently have a steadily rising work load without any concomitant increase in staff numbers it is unlikely that adoption of a policy of universal testing by HPLC would lead to a reduction in staff numbers. It is more likely that the investment in new technology would lead to highly skilled staff being freed from repetitive manual work to perform other important tasks. It can reasonably be anticipated that the costs of HPLC will continue to fall whereas staff costs will not. The shift of laboratories to this technology is likely to continue, particularly in countries with relatively high labour costs.

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