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Review

Executive summary

Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research

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Introduction

The haemoglobinopathies (thalassaemias and sickle cell disease (SCD)) are inherited disorders of haemoglobin.

In 1993, the UK Standing Medical Advisory Committee made the following recommendations.

- Preconceptual carrier diagnosis for these conditions should be encouraged.
- Antenatal and neonatal screening should be universal in districts where over 15% of the population are from ethnic minorities.
- Specialist counselling should be integral to such programmes.

Although generally welcomed, these recommendations received little attention, possibly because they were not firmly evidence based and were issued as Health Service Guidelines, which did not oblige purchasers or providers to take action.

Objectives

The objectives of this review were:

- to review the literature on haemoglobinopathy screening
- to review the literature on gene prevalence in the various British populations for the sickle and β-thalassaemia genes
- to apply these to Census data in order to develop evidence-based estimates for the prevalence of SCD and β-thalassaemia in England
- to evaluate local data from North West London (Brent) to illuminate debate regarding the outcome of haemoglobinopathy screening programmes and their costs.

Methods

A systematic literature search was undertaken and maintained up to date during preparation of the review. Two or more members of the team reviewed all references. The data relating to the ethnic prevalence of abnormal haemoglobin genes were collected, graded and applied to Census data in order to derive estimates for the prevalence of the haemoglobinopathies in England. These data were validated against all the present English population screening programmes for haemoglobinopathies.

Additional data were collected prospectively from the district of Brent, North West London, on workload and outcomes of antenatal and neonatal screening and follow-up, in order to perform economic analyses.

This approach was then exploited further by combining the prevalence data with an extrapolation of a neonatal haemoglobinopathy screening cost-effectiveness model.

Results: systematic review

The haemoglobinopathies

The haemoglobinopathies are autosomal recessive defects. A distinction is made between carriers (who have only one affected globin locus and remain healthy throughout life, but are at risk of transmitting the disease to their descendants) and people who are homozygous, or doubly heterozygote, for a disorder.

The number of people in the UK who have SCD is rising and is expected to be in excess of 10,000 by the year 2000. Carriers are predominantly Afro-Caribbean and sub-Saharan in origin, but Arab, Mediterranean and Indian peoples are also affected.

There are approximately 600 people with β-thalassaemia major in the UK. It is most common in Mediterranean, Indian, and Pakistani peoples. Alpha-thalassaemia is most common in South-east Asia, Hong Kong and China, with α-thalassaemia major being incompatible with life.

The management of SCD is based on routine prophylactic penicillin for infants and the early use of antibiotics to prevent overwhelming infection.

Thalassaemia treatment is mainly through regular blood transfusions and splenectomy once hypersplenism develops.

Screening

A variety of models of haemoglobinopathy screening exist within Britain, and the service is patchy and often unstructured. Screening programmes may be opportunistic or systematic, targeted or population based. In targeted programmes, consideration needs to be given to the criteria for selection and the population base.

Antenatal screening allows women at risk to make informed decisions about reproduction. It aims to detect carriers, provide genetic counselling, and offer carrier couples the choice of parental diagnosis and selective abortion.

The primary aim of neonatal screening is to identify babies with SCD and commence life-extending prophylactic penicillin and comprehensive care. There is no equivalent reason for the early diagnosis of β-thalassaemia major, and β-thalassaemia trait is not identified by neonatal tests. However, screening does permit genetic counselling for parents with affected or carrier newborns.

In terms of the acceptability of antenatal screening, most British evidence is derived from studies at tertiary prenatal diagnosis centres and termination is more likely for β-thalassaemia major than for SCD, for which the prediction of severity is not feasible.

Cost-effectiveness

Attempts to measure the impact of British neonatal screening programmes have focused on groups of women attending tertiary referral centres for prenatal diagnosis, and the experience of US community-based programmes has shown that these findings may not be generalisable at the population level.

There is no published study reporting the full benefits of neonatal screening for the haemoglobinopathies, although two American studies have examined the cost-effectiveness of neonatal hospital screening.

Laboratory methods

The haemoglobinopathies can be detected by biochemical testing or DNA analysis. Biochemical methods include isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). Some commentators favour HPLC for large-scale screening programmes. It is recognised, however, that IEF provides more information because of its high resolution.

Results: supplementary research

Prevalence

Prevalence estimates were derived from country rates, and validated and adjusted where necessary for application to the UK. Estimates were derived for β-thalassaemia, and haemoglobin S, C and E traits. The proportions of births with clinically significant disease were calculated using the Hardy–Weinberg equation.

The authors estimate that 17 (0.03/1000) infants are born each year in England with β-thalassaemia major or intermedia, even when allowing for terminations, and 160 (0.25/1000) with SCD.

Outcomes of universal antenatal screening

Using the Central Middlesex Hospital programme for sample data, it was found that unselected women at risk of SCD are significantly less likely to have their partners tested or to accept prenatal diagnosis than tertiary referrals. This was not the case for those at risk of β-thalassaemia; 80% of β-thalassaemia and 16% of sickle cell anaemia births are prevented by universal screening. It is likely therefore that previous British studies have overestimated the impact of universal antenatal screening in preventing SCD births.

Cost-effectiveness of antenatal screening

From the study of Central Middlesex Hospital data, the authors suggest that, in addition to offering genetic choice, a universal antenatal screening and counselling programme is likely to be considered cost-effective at least in areas with haemoglobinopathy traits ≥ 2.5%, especially if a high proportion of these are β-thalassaemia.

Cost-effectiveness of neonatal screening

The results suggest that screening services should aim to cover populations that generate a workload of over 25,000 births per year, and preferably over 40,000. IEF and HPLC are very similar in terms of average cost per test.

At 16 sickle traits/1000 and 0.5 SCD/1000, there is no significant difference in the detection component cost between universal and targeted programmes. Below this prevalence, a targeted programme is cheaper but is likely to miss cases.

The key issue for commissioning organisations is the incremental cost-effectiveness of identifying one extra case of SCD with a universal programme. These costs are provided at different levels of prevalence.

Cost-effectiveness of neonatal screening follow-up

The integration of nurse specialist follow-up for the purposes of counselling and education within the neonatal screening service resulted in the counselling of 91% of families whose infants had been identified with a clinically significant haemoglobinopathy or trait. Costing information suggests that there may be significant value in the intensive style of follow-up employed by this programme.

Conclusions

Implications for health care

- The evidence supports previous national guidance (Standing Medical Advisory Committee) that commissioners should develop appropriate population-based haemoglobinopathy screening programmes (review).
- Because this study makes no comparison with other programmes, the generalisability of the cost models on which the conclusions are based could usefully be considered in the planning process. Other programmes may have very different structures and therefore costs (study).
- There is currently little cooperation between health authorities and across regions. The evidence suggests that the creation of partnerships when building programmes would ensure efficiencies of scale and expert input, while maintaining closeness to the clinical services (study).
- Commissioners are not currently required to have a quality framework for any implementation plan for their screening programmes. Such a plan would include the linkage to and provision of both counselling and specialist care (review).
- This review suggests a need for all haemoglobinopathy screening programmes to have defined paths of responsibility for every aspect of the work, with agreed service standards for the purpose of audit (review).
- Audit depends on outcome measures (including timetables) being defined for the respective screening processes (study).
- The indications are that there is a need to address the current lack of systematic data collection in this area, particularly:
  - ethnic monitoring (for instance, there is no standard instrument currently used in laboratories to record ethnic group or ethnic origin)
  - ethnic-specific data on screening uptake
  - patient registries to monitor long-term outcomes and mortality (study).

Neonatal screening

- The analyses demonstrate that, for laboratories to be cost-effective, they should be able to screen at least 25,000 births annually (study).
- For areas where there are 16 sickle cell trait and 0.5 SCD cases per 1000 births, the data suggest that universal screening is cost-effective (study).
- In areas where there are fewer births, consideration of value for money and equity is of importance. In those areas where 7–15 per 1000 births have sickle cell trait, universal screening would be justified (study).
- The evidence supports the development of systems to inform parents of their baby's test results and to enter children with major haemoglobinopathies into specialist comprehensive care services (review).
- A national external quality assessment scheme for neonatal haemoglobinopathy screening would be able to address issues of quality assurance (study).

Antenatal screening

- According to the results, universal antenatal screening is cost-effective for all districts having 1% ethnic minorities if 25% of those carry the β-thalassaemia trait (study).
- An important outcome indicator is genetic choice, so some commissioners would purchase services at a lower prevalence in their population (review).

Recommendations for research

The authors' main recommendations for research include:

- study of the disbenefits and potential harms of screening for haemoglobinopathies at any stage
- optimal methods and modes of delivery of counselling for the haemoglobinopathies
- the attitude of the various communities in Britain to risk relating to haemoglobinopathies and how this impacts on the counselling process
- study of the equity and access issues relating to haemoglobinopathy screening, particularly as they relate to race
- the most cost-effective ways of delivering specialist haemoglobinopathy services.

Additional recommendations for research are made within the text of the report.

Publication

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel and funded as project number 93/33/03.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work either prioritised by the Standing Group on Health Technology, or otherwise commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

Copies of this report can be obtained from:

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