Screening brief

Antenatal screening for sickle cell disease

The disorders

- A group of autosomal recessively inherited disorders resulting from production of abnormal globin in the β chain of haemoglobin. Inheritance of the sickle β globin gene (Hb S) from both parents gives rise to sickle cell anaemia (Hb SS). In compound heterozygotes (such as Hb SC disease), where an S gene is inherited from one parent and another interacting haemoglobin variant such as C, D^{Punjab}, E, or O^{Arab} is inherited from the other parent, similar (though sometimes less severe) clinical problems arise. Coinheritance of S and a β thalassaemia gene (causing deficient production of a β chain) can be as severe as Hb SS.

Prevalence of sickle cell disease

- There are about 200 affected pregnancies a year in the UK.[1]
- In the UK, sickle cell disease is most common in black African and black Caribbean populations, affecting about 1% and 0.5% of such pregnancies, respectively.[1 2]
- Very rare in northern Europeans (about 1 per million pregnancies),[1 3–4] it is common in parts of the world where malaria was, or is, endemic—for example, areas of India, the Middle East, and Greece, as well as Africa and the Caribbean.

Prognosis

- Chronic haemolytic anaemia (Hb 6–8 g/dl); some patients need regular blood transfusions. Risk of some bacterial infections is high. Clinical course is dominated by crises of various types. These include painful crises (pain is the dominant clinical problem)—episodic severe bone and joint pain due to thrombo-occlusive events (including stroke in childhood and pulmonary sickling), other thrombo-occlusive crises, aplastic crises, and sequestrian crises where a large proportion of the red cells are trapped in the spleen or liver. End organ damage may result in blindness, renal failure, or hip destruction. Usual causes of death are acute infection in children and hypoxic crises in adults.
- Mortality rates: compilation of age-specific death rates indicates that for Hb SS, median age at death is 42 for men and 48 for women; for SC disease, median age for death is 60 for men and 68 for women.[5]

Screening

- The first step is to ask the mother explicitly whether she or the father of the child have any origins from parts of the world where malaria disease is, or was, common. This is commonly called selective antenatal screening, but determining ethnic origin is a screening test, so in fact all women are screened.
- In the UK, screening would involve the identification of couples with black African or black Caribbean origins. A checklist of other countries can be used to achieve a higher detection rate, but at the cost of complexity and, therefore, poor compliance. In the UK it has been recommended, without full justification, that any parent who has non-northern European origins should be carrier screened.
- Carrier testing is done by blood test, usually by haemoglobin electrophoresis or by high performance liquid chromatography (HPLC) to detect abnormal bands.[2] Newer capillary electrophoresis techniques are cheaper than HPLC. These tests detect approximately 99% of carriers.
- The father is tested if the mother is a carrier of the S gene, β thalassaemia, or other important defects of the β chain globin. If he too is a carrier of one of these, there is a one in four chance of the fetus being affected, and prenatal diagnosis is offered to the couple.
- Screening performance: with complete uptake the detection rate is over about 95% (though this is poorly documented) and the false positive rate is approximately the prevalence of ethnic groups offered further testing.
- Haemoglobin electrophoresis may be recommended for all pregnant women in communities where a high risk ethnic group constitutes more than a certain proportion (for example, 15%) of the childbearing population. However this has not been judged to be cost effective in the UK.[2] It would, however, apply to communities in which the disease is endemic (that is, northern Greece, southern Italy, Bahrain, and parts of India).

Antenatal diagnosis

- Antenatal diagnosis is usually by chorionic villus sampling (or rarely amniocentesis) in early pregnancy, with DNA analysis using PCR for sickle and other β gene mutations. Preimplantation diagnosis is now becoming feasible and may become more widely available.[6]

Intervention

- Counselling; offer of termination of an affected pregnancy.

Overall assessment

- In communities where sickle cell disease occurs almost exclusively in ethnic minority groups, screening is worthwhile by identifying couples in which at least one partner has non-northern European origins, and performing haemoglobin electrophoresis, firstly on the mother and then on the father, if the mother is positive.
- In communities where sickle cell disease occurs commonly in the predominant ethnic group, screening is worthwhile by offering haemoglobin electrophoresis to all pregnant women.

1 Hickman M, Modell B, Greengross P, *et al*. Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *Br J Haematol* 1999;**104**:860–7.
2 Livingstone FB. Frequencies of hemoglobin variants. Oxford: Oxford University Press, 1985.
3 Sickle cell disease guidelines panel. *Sickle cell disease: screening, diagnosis, management and counseling in newborns and infants*. Clinical Practice Guideline, No 6. Maryland: US Department of Health and Human Services, 1993.
4 Platt O, Brambilla D, Rosse W, *et al*. Mortality in sickle cell disease. *N Engl J Med* 1994;**330**:1639–44.
5 Zeuner D, Ades A, Karnon J, *et al*. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. *Health Technol Assess (Rockv)* 1999;**3**:1–186.
6 Xu K, Zhong S, Veeck L. First unaffected pregnancy using preimplantation genetic diagnosis for sickle cell anaemia. *JAMA* 1999;**281**:1701–6.