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Review

Executive summary

Screening for cystic fibrosis

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Executive summary

Background

Cystic fibrosis (CF) is a common serious inherited disorder associated with considerable morbidity and high case-fatality. Two recent developments have implications for screening policy, the discovery of the gene responsible for the condition and the continuing improvement in life expectancy.

Aim

To provide the information needed to help decide whether screening should become routine and, if so, which strategy to adopt.

Methods

The review is based on a literature search of electronic reference databases of published and 'grey' literature together with handsearching of the most recent publications.

Results

Treatment

CF is a disorder in which the exocrine glands of the epithelia produce abnormally thick secretions of mucus and elevated sweat electrolytes. It is characterised by progressive respiratory and gastrointestinal problems, and is associated with impaired fertility. There is substantial variability in severity, with some patients symptomatic at birth, while others may not present for months or even years.

Modern treatment with physiotherapy, antibiotics and enzyme supplements delays disease progression and survival rates are now predicted to exceed 40 years. Newer treatments, including anti-inflammatory agents and gene replacement therapies, may eventually lead to even greater longevity. However, research is still in its earliest stages and success is not guaranteed.

Genetics

It has been known since the 1940s that CF was an autosomal Mendelian recessive disorder and, in 1989, the transmembrane conductance regulator (CFTR) gene situated at 7q31, was shown to be responsible for the condition. The gene spans over 250 kb and comprises 27 exons; the mRNA transcript is 5 kb long and codes for a protein which controls the electrochemical balance of chloride secretion and sodium absorption.

To date over 800 mutations in the CFTR gene have been identified, although not all are disease causing. The most common mutation in the UK is the three base pair deletion, ΔF508, which accounts for 75% of carriers; three commercial multiple-mutation assays are available that can detect about 86% of carriers in Scotland, Wales and the North of England, or 80% elsewhere. Different proportions apply to Asians (35%), Ashkenazi Jews (95%) and Blacks (41%).

The UK birth prevalence is 1 in 2400, which implies a carrier frequency of 1 in 24. A carrier couple have a one in four risk that each of their children has CF; this is reduced to under one in 50,000 if neither parent has a detectable mutation. When only one parent is a carrier the risk is about 1 in 500.

Genetic screening

The aim of genetic screening for CF is to reduce the birth prevalence of the disorder. This is principally achieved by identifying carrier couples who can have prenatal diagnosis and selective termination of pregnancy. Other options are to: avoid pregnancy; change partners; have artificial insemination using donor sperm or egg; and have pre-implantation diagnosis to select unaffected zygotes.

Carrier couples can be identified directly during pregnancy or when it is being planned, or indirectly by determining the carrier status of everyone of reproductive age in the population. A third approach is systematic 'cascade' testing within CF families.

Antenatal and pre-conceptional genetic screening

There have been 11 published studies reporting the results of antenatal screening pilot projects. The combined results on over 40,000 tests

demonstrate the feasibility of the method, and show the acceptability of screening (uptake 74%) and invasive prenatal diagnosis in carrier couples (uptake 89%).

Pre-conceptional CF screening has been tried at a family planning clinic setting with high uptake. Pre-nuptial testing is already available for orthodox Ashkenazi Jews. Pre-implantation diagnosis is currently being carried out at six licensed UK centres, although worldwide less than 100 procedures for CF have been performed.

Other genetic screening

Four general population screening studies have been carried out in general practice with a total of almost 11,000 patients. Uptake was only 8% when invited by letter but 48% when approached opportunistically in the clinic. Uptake was also low when screening was offered to school students (41%, 42% and 70% in three studies), in the workplace (21%) and as the result of a general community-wide campaign (8%).

Usually probands are told that close relatives can be screened but only one-third of first- and one-tenth of second-degree relatives are tested. There have been three studies of the more active cascade screening approach. Uptake was higher and a large proportion of those tested were carriers. However, mathematical models have shown that under 15% of carriers in the population would be detectable this way.

There is also experience of screening in selective groups such as those already having invasive prenatal diagnosis unrelated to CF, and in assisted reproduction units for infertile men and sperm donors.

Neonatal screening

This aims to bring forward the diagnosis of CF and so improve prognosis. The detailed experience of neonatal CF screening has been reported for 20 programmes including six in the UK. Protocols vary: single or repeat testing; foetal blood spots or meconium; immunoreactive trypsinogen (IRT) or DNA. In total more than five million neonates were screened with a low false-positive rate (0.5 per 1000), acceptable detection rate (90%), and favourable positive predictive value (33%).

The ability of screening to alter long-term prognosis has not been conclusively proven. Two randomised trials of screening, five case–control studies, a study of sib-pairs and a trial of prophylactic versus symptomatic treatment of early disease all provide relevant information. However, this is either predominantly short term or subject to strong statistical bias. Nevertheless there is some circumstantial evidence favouring a benefit.

Human and financial costs

Screening may result in psychological harm and, if invasive prenatal diagnosis is involved, there is an approximately 1% risk of foetal loss. The cost of antenatal screening is estimated to be between £46,000 and £53,000 per CF pregnancy detected, considerably less than the lifetime cost of treatment. Neonatal screening costs about £4400 per case detected or £6400 for those who would not otherwise have had an early diagnosis, and about £1500 and £2200, respectively, when combined with antenatal screening.

Conclusions

Evidence supports the following actions:

- antenatal genetic screening should be offered routinely
- pre-conceptional genetic screening should be made available for couples who request it
- genetic screening should be available for infertile men and for sperm donors
- testing should be undertaken in laboratories with an annual throughput of at least 5000 CF tests
- health authorities could consider introducing neonatal screening.

Recommendations for future research

- Re-analysis of the Wales and West Midlands neonatal screening trial.
- More research on psychological and medical consequences for carrier detection in neonatal screening.
- Neonatal screening programmes to undertake RCTs of specific early treatments.
- Innovative methods for presenting information on genetic screening.
- Audit procedures to ensure that parents give informed consent to neonatal screening.

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 93/32/03.

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.

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.

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