Neonatal screening for cystic fibrosis: present and future

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Despite there being effective tests for detecting cystic fibrosis (CF) using newborn screening blood samples, screening in neonates has not had universal approval because of uncertainty about its benefits. After up to 18 years experience, at a recent conference in Caen several aspects attracted universal agreement. There is still major delay in clinical diagnosis after the onset of symptoms. There is short-term benefit in early diagnosis by screening, with reduced morbidity in the first 2 years, evidence of significant nutritional benefits up to the age of 10 years, and probable respiratory benefit over this time frame. There is great potential for research into treatment modalities and no evidence of significant psychological harm to CF babies from early diagnosis. With a screening protocol that includes a DNA test there is some unwanted carrier detection and careful genetic counselling is needed. There is no evidence yet that screening will extend the life of CF patients, so some doubts remain as to its overall effectiveness, and there have been no good studies on comparative costs in screened and unscreened cohorts. Even so, the weight of evidence suggests very worthwhile advantages for screened babies and their families. Because of this, it is unlikely that further trials will take place. It may be that the onus now is on those who do not support screening to justify this stance to parents who may favour it.

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and although it is clearly not high for carriers in general, the carrier babies identified by newborn screening may be a subset with different risks.

Since the 1996 meeting of the International Society for Neonatal Screening, the clinical advantages of neonatal screening have become somewhat more clearly defined. Delay in diagnosis and the high prevalence of early, treatable, symptoms has been well documented and accepted for some time (9). It is also clear that without screening a significant number of CF children remain undiagnosed until after the birth of a second affected child in the family (10). Two publications about outcome (a randomized controlled trial and a carefully conducted observational study) have now demonstrated that effects on nutrition (11, 12) and lung function (12) persist to at least 10 y. While the former study has been criticized, (13), an expanded analysis of the data strengthens the findings that there are indeed significant nutritional advantages persisting to 10 y of age for the screened population.

Neonatal CF screening now seems to fit the generally accepted criteria for screening. Classical CF is a clinically and biochemically well-defined disorder, with significant morbidity and mortality. There is effective (but not at present curative) treatment available which over two-thirds of children there is an interval before significant morbidity and mortality. There is effective clinically and biochemically well-defined disorder, with be a subset with different risks.

The Fifth International Conference on Neonatal Screening for Cystic Fibrosis was held in Caen in September 1998 (17). There was general agreement that:

1. There is significant delay in clinical diagnosis;
2. There are important early symptoms in CF patients;
3. There is sustained benefit in early treatment;
4. There is a great potential for research into effectiveness of therapies;
5. There is a good screening test: IRT + CFTR gene analysis.

It was also agreed that there was little demonstrated harm from newborn screening, other than the unwanted carrier testing discussed above. Despite these agreements, the occurrence of CF testing in newborns has altered little in recent years: testing was carried out in about 6% of neonates in the USA, 22% in the UK, 13% in France, 24% in Italy, and much smaller percentages elsewhere. Only in Australasia (92%) is it popular.

What does early diagnosis represent? Of course, it provides an opportunity for early treatment. It enables the avoidance of delayed diagnosis, with the accompanying angst for the parents, as they feel that their child has a problem not properly understood by their doctor. It enables avoidance of misdiagnosis, such as several years of treatment for “asthma”. It enables appropriate and timely genetic counselling. It is intelligent medicine. Care at a CF treatment centre has been shown to provide superior management with better outcome (18) and it seems incontrovertible that there are early benefits to patients from diagnosis by screening. Thus, the ideal future management of CF seems to comprise newborn screening and early referral for treatment to a CF treatment centre. Certainly, there is absence of proof of improved survival, but survival is not an appropriate outcome measure for comparing screening with clinical diagnosis. This is because, first, a benefit would not become apparent for some decades and, secondly, benefits may relate to factors other than longer survival. If health in the first decade (or more) were to be improved, this would be a significant advantage even if overall survival were not extended.

Since the 1996 meeting of the International Society for Neonatal Screening in Boston, various national bodies have made recommendations about neonatal screening for CF. In 1997, the Center for Diseases Control in Atlanta, Georgia, USA, held a consensus conference on this subject. It was concluded that the
information “justifies state-wide studies, especially of the impact of delayed nutritional, neurodevelopmental and cognitive outcome, and potential benefits of CF center care” and that further state-based pilot studies of screening would be appropriate (19). In the UK, one Health Technology Assessment found that “neonatal screening for cystic fibrosis should be encouraged”(5) and another that “Health authorities could consider introducing neonatal screening”(20). In contrast, the 1997 National Institutes of Health (USA) consensus conference on carrier testing for CF stated that neonatal screening was not recommended, because of lack of evidence of efficacy (21). It is important to note that neonatal screening was not the subject of this consensus meeting and the finding on neonatal screening seems to have been made without due consideration of the evidence. Further randomized controlled trials seem unlikely. Those who, like the present authors, favour neonatal CF screening find the evidence for overall benefit to be strong. Perhaps the onus should now be on those who feel that it is not justified to explain to parents why this evidence is not yet strong enough.

References