Cystic fibrosis and deafness

During our preliminary molecular survey of the cystic fibrosis (CF) ΔF508 mutation in 18 patients selected by positive sweat tests, we found one patient with agenesis of the cochlea (Mondini's syndrome), several bouts of dehydration, and absence of pulmonary digestive complications. This 12 year old girl was born to unrelated, non-Caucasian parents and a heterozygous ΔF508/ non-ΔF508 genotype was found in her lymphocytes. In our study only 33.5% of patients were found to be homozygous for the classical CF mutation, 11.8% were heterozygous, and the remaining majority of patients were not carriers of the ΔF508 mutation. As expected in our mixed non-Caucasian population, several other combinations of CF mutations may be found in a rather different distribution compared to European countries. Recently, Raskin et al. showed that 46% of their patients in a more homogeneous racial region of Brazil were homozygous for the ΔF508 mutation. As a consequence, minor and uncommon clinical presentations of CF would be expected to occur in our population. Our patient with sensorineural deafness as a result of agenesis of the cochlea had no other clinical features that could be attributed to a similar mechanism to, for example, congenital agenesis of the vas deferens in intersex males, in whom CF mutations have recently been reported.1 It is also possible in our population that CF patients may be found more frequently in different clinics seeking medical attention for other reasons than those expected in classical CF patients.

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1 Raskin S, Phillips JA III, Kaplan G, et al. DNA data suggest that the CF trait in Brazil is not as frequent as is believed, and that the frequency of the CF allele is tenfold more than observed. Am J Hum Genet (Suppl) 1992;51:A342.

Approaches to prenatal cystic fibrosis carrier screening

Two general approaches to the detection of cystic fibrosis (CF) heterozygotes in the antenatal clinic have been proposed: couple1 and two step2 screening. Miedzybrodzka et al3 suggest a variant, termed disclosure couple screening. It differs from the original concept of couple screening in that results of testing are fully disclosed to all participants. In our trial of couple screening,4 we report back in detail how people respond to a disclosure couple screening approach. The CF allele and a 1 in 4 risk of affected outcome. All others (only one partner tested, both tested) with a CF allele are given a composite residual risk of a CF child. With 85% of CF alleles detectable, this is 1 in 800.

Contrary to our initial expectations, the take up rate of couple screening has been almost as high as that for testing (67% versus 71%). Its cardinal virtues are simplicity and economy. The main problem in two step screening has been the time that must be devoted to the skilled counselling of CF carriers, one in every 26 participants even at an 85% detection rate.2 If this form of CF screening is to become part of routine obstetric care (as a goal of pilot trials), there will need to be a trained counsellor in every maternity hospital. A similar problem confronts disclosure couple screening. In contrast non-disclosure couple screening can be effectively operated by existing midwife staff and the rare 1 in 4 risk couples referred to a consultant obstetrician. In support of this statement is the fact that our two step screening trial has now been discontinued at the obstetrician’s request and replaced by non-disclosure couple screening.

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This letter was shown to Dr. Miedzybrodzka et al, who reply as follows.

Professor Brock favours non-disclosure couple screening over two step screening on economic grounds, as two step screening requires satisfactory counselling of carriers and causes maternal anxiety until a partner’s result is available. Nevertheless, we believe that carrier information may be of benefit to those screened, giving information for future pregnancies with different partners and allowing relatives to be counselled. Careful research can show that those screened and their families do not benefit from information provided by good counselling of carriers, that we believe that carrier is an ethical necessity. We accept that counselling of carriers requires resources, but, especially as the population becomes more aware of genetic risks, it allows targeting of genetic information to those at high risk. Disclosure couple screening would allow carrier information to be of benefit, but the anxiety associated with two step screening might be decreased as partners’ results would be immediately available.3

The Edinburgh finding of no difference in uptake of the two forms of screening mirrors the results of our own randomised trial of couple v two step screening (91% uptake of two step screening v 89% for couple screening).5 One of the full results of our psychological and economic evaluation are available we will be able to comment further on the suitability of different approaches to screening.

Although high uptake does provide the need for counselling of detected carriers, proper counselling and explanation is still required to allow couples to give informed consent to carrier testing.5 To obtain truly informed consent to a screening test is unethical and exposes a health authority to risk of litigation. Carrier testing must be explained to staff who fail to understand its advantages, limitations, and drawbacks.

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Severe cystic fibrosis in a child homozygous for the G542 nonsense mutation in the CFTR gene

Several homozygous nonsense mutations in the CFTR gene (S125X, G542X, W1316X, R553X, G542X, G542X, R553X, and R553X) have been reported.6 These patients were mildly affected, suggesting that the nonsense mutation alone may lead to mild expression of the disease, particularly mild lung symptoms.6,7 Some hypotheses have been proposed to explain the minor pulmonary involvement in comparison to the severe pancreatic dysfunction in these patients: (1) the possible presence of tissue specific RNA splicing minimising the effect of the nonsense mutation, (2) residual function of the truncated protein in certain tissues such as lung, and (3) the partial substitution of the missing function by alternative pathways occurring only in pulmonary epithelium.8 None of these explanations has yet been substantiated. These papers suggested that the lack of CFTR protein in airway cells may be less damaging than the presence of a structurally abnormal protein. This is in contrast to many monogenic diseases, such as haemophilia, in which the presence of nonsense mutations is frequently associated with severe phenotype. The picture when compared to that associated with missense mutations.7 In these cases, nonsense mutations cause severe illness because the truncated protein is toxic. Under treatment with pancreatin enzymes, the clinical course improved but nutritional indices remain low. Lung function as expressed by the forced expiratory volume in one second (FEV1) was started. Haemophilus influenzae was first isolated from sputum cultures, then Pseudomonas aeruginosa and Klebsiella. After 15 days of IV treatment with cephalosporins and aminosides, followed by aerosol colimycin, his pulmonary state improved. Abundant stools improved.

A homozygous G542X mutation was found by DGGE and identified by exon 11.