Screening for carriers of cystic fibrosis—a general practitioner's perspective

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The identification of the gene for cystic fibrosis has led to the possibility of population based screening for carriers of cystic fibrosis to identify couples at risk of having an affected child. Pilot studies have shown that screening is feasible and does not cause untoward anxiety, though the uptake of testing varies considerably with the setting and method of invitation. Screening offered at times when individuals (and health professionals) perceive it as directly relevant will probably gradually become established in the United Kingdom.

This review examines the role of general practice in genetic carrier screening as exemplified by cystic fibrosis. General practice has a pivotal role from the beginning in providing individuals and couples with information, facilitating testing of patients' relatives and of carriers identified by screening elsewhere (such as antenatal clinics), and offering testing in the context of reproduction. Screening for the cystic fibrosis gene will probably be followed by other genetic screening programmes.

Cystic fibrosis, the commonest serious inherited disease in northern Europe, frequently leads to death in early adult life. It is inherited as an autosomal recessive condition with a carrier frequency of about 4·3% in the United Kingdom.[1] One partner is a carrier in 1 in 12 couples. In 1 in 540 couples both partners are carriers and have a 1 in 4 risk in each pregnancy of producing an affected child; very few such couples have a family history of cystic fibrosis. Over 200 mutations have been described since the gene for cystic fibrosis was identified in 1989.[2,3]

Carriers can be detected by examining DNA from a mouthwash, and laboratories that test large numbers of people can identify the four commonest mutations, which account for 85% of heterozygotes. Screening is non-invasive and there are no false positive findings, but 15% of carriers give a negative result on screening. Thus the present frequency of detectable carriers of cystic fibrosis is about 3·7% and of detectable carrier couples 1 in 730—74% of those actually at risk. It is theoretically possible to identify, and offer prenatal diagnosis to, three quarters of carrier couples.

This article discusses the pivotal role of general practice in such cystic fibrosis screening programmes.

Why screen for carriers?

The main objective of screening is to identify carriers and carrier couples, ideally before pregnancy, and inform them of their risk of having an affected child. They then have a range of options, including ignoring the information, not having children, or using prenatal diagnosis. Most couples choosing prenatal diagnosis for cystic fibrosis (as for other genetic diseases) decide on abortion if the fetus is affected and subsequently have another pregnancy in an attempt to achieve the desired family size (D Williams, personal communication). However, the autonomy of the couple is paramount, and couples who decide against prenatal diagnosis or choose to continue an affected pregnancy must be supported in their choice.

The prognosis of cystic fibrosis is improving and many affected adults live independent and productive lives,[4] but management is harrowing, and, despite the prospect of gene therapy, the outlook is unlikely to improve sufficiently in the foreseeable future to invalidate a preventive approach to the disease.

On the other hand, the situation with regard to cystic fibrosis screening is not ideal. A quarter of carrier couples will be missed, and screening for an occult problem in healthy people can damage a person's self image. Therefore a number of projects, mainly funded by the Cystic Fibrosis Research Trust, were set up to examine whether screening does more harm than good—for example, by causing anxiety—and to test the feasibility, acceptability, and cost implications of screening in various settings.

How can carrier couples be identified?

BY HAVING AN AFFECTED CHILD

As most families in the United Kingdom have fewer than two children only about half of carrier couples will be identified because they have a child with cystic fibrosis (1 in 4 risk in each pregnancy). Though they can be offered prenatal diagnosis in subsequent pregnancies, many will have completed their family by this time.

BY STUDYING PATIENTS' RELATIVES

Many relatives of an affected child will be carriers (table I). Family studies can identify a wider range of carriers than general population screening because some patients carry an identified rate mutation, which can then be included with the common ones when testing relatives. Super *et al* tested 397 first degree relatives of patients with cystic fibrosis (excluding parents) and identified 194 carriers (1 in 2 tests) and five carrier couples (1 in 120 tests), all of whom requested prenatal diagnosis.[5] At best, however, family studies could identify less than 5% of the carriers in the country.

BY POPULATION SCREENING, FOLLOWED BY TESTING PARTNERS AND RELATIVES

Screening the general unselected population is not an efficient strategy. If on average one carrier is detected for every 30 people tested, 30 partners of carriers must be tested to identify a couple "at risk." As some carriers are single, over 1000 people must be screened to identify a carrier couple. Efficiency can be improved by offering testing to carriers' relatives, whose average risk is about half that of patients' relatives (table I). Testing a carrier's parents can

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show which side of the family is affected: these relatives have the same risk as the relatives of patients with cystic fibrosis.

The best approach for identifying a high proportion of carrier couples and permitting reproductive choices before the birth of an affected child seems to be population screening, coupled with testing the relatives of carriers (cascade screening).

There is considerable debate on when and where population screening for carriers should be done (table II). However it is done, general practitioners have an important role because the detection of a carrier always indicates a family who may need to be followed up by the general practitioner.

A variant of antenatal screening is to offer testing to women who attend their general practitioner for confirmation of a pregnancy, usually about four weeks earlier than their first hospital antenatal appointment.[6] Another variant, proposed on grounds of efficiency, is "couple screening" during pregnancy.[7] The test is done only if both partners provide a sample, and only couples where both are shown to be carriers and can be offered prenatal diagnosis are considered to be "screen positive." All others are considered to be "screen negative" and informed accordingly. However, this approach excludes cascade screening for couples who screen negative even though one is found to be a carrier.

Why screen in general practice?

The organisation of general practice in the United Kingdom seems well suited for screening in the community. Nearly everybody is registered with one of over 30 000 general practitioners who serve the whole country. General practitioners are family doctors and family studies form the basis of genetic practice.[8] Most practices have an age-sex register (an essential database for the provision of screening), and the 1990 general practitioner contract increased the emphasis on screening and surveillance.

A typical practice of 10 000 patients includes up to 370 detectable carriers of cystic fibrosis, half of reproductive age. However, it is not necessary to screen all these 5000 people to identify the majority of carriers if cascade screening is performed. For example, while Bekker *et al* were screening in a large inner city practice 20 relatives of a patient with cystic fibrosis registered with a neighbouring practice requested testing, and six carriers were identified, including one carrier couple.[9]

TABLE I—*The chance of being a carrier (%) for different degrees of relatives of patients and carriers*

Relative	Of a patient	Of a carrier
Son or daughter	100	50
Sibling	66	50
Parent	100	50
Uncle or aunt	50	25
Cousin	25	12·5

TABLE II—*When and where should screening be offered?*

	Advantages	Disadvantages
Antenatal clinics	Targets group immediately at risk Specimen collection system already in place Cascade screening possible with cooperation of general practitioner	Detection of carrier couples may be too late for first trimester prenatal diagnosis in presenting pregnancy, or prenatal diagnosis at all Decisions must be taken quickly Increased anxiety in pregnant carriers until result of partner's test available Reinforces false belief that only women likely to have a genetic problem
General practice (adults of reproductive age)	Nearly all population accessible Before choice of partner or reproduction, therefore allows carrier couples time to reflect after counselling before making reproductive decisions Cascade screening of relatives possible	Costly option Unlikely to be systematic as many people will not perceive testing to be relevant Misses those without general practitioner Health professionals find it difficult to introduce and explain the subject Often long time lag before reproduction; this may lead to individuals forgetting result
School	Total population accessible Before choice of partner or reproduction Both sexes tested Makes teaching of genetics and biology more relevant	Costly option Hard to preserve confidentiality May damage "healthy" self image of a carrier at vulnerable time of life Fear of stigmatistion May not be seen as relevant Often long time lag before reproduction
When giving family planning and preconception advice	Often relevant, therefore individual not likely to forget result Before reproduction	Limited target population—mainly women
Neonatal	Total population accessible Blood spots already collected Will also identify most homozygotes Both sexes tested	Identifies less than half of carrier couples in time to avoid an affected child (a quarter of the offspring will not be carriers, and quarter will have the disease) Very long time lag before reproduction

Results of pilot screening projects

What actually happens when people are offered testing? Pilot studies in antenatal clinics, family planning clinics, and general practice found no evidence that those with a negative result were perturbed or that there was significant lasting anxiety among the carriers detected.[9-12]

Uptake of testing varied considerably with setting and method of invitation. It was 87% among women attending a family planning clinic[11] (though most family planning consultations take place in general practice rather than community clinics); 84% among eligible pregnant women attending an Edinburgh maternity hospital; and about 90% among eligible pregnant women attending their general practitioner for the booking appointment.[12 13]

In studies of general population screening in primary care testing was offered to (non-pregnant) people of reproductive age both by invitation and opportunistically. Uptake was only 4-12% among those invited by letter and 17% among those handed an information booklet about the test by the receptionist. A high uptake (70%) was achieved only when the researcher approached people in the waiting room, gave them a booklet and explained the project, and offered immediate testing[9]—a labour intensive and time consuming approach.

Screening the whole non-pregnant population is relatively inefficient and expensive: Bekker *et al* had not identified any carrier couples after amost 1000 tests,[9] while antenatal screening of 3409 pregnant women led to the detection of five carrier couples, who all requested prenatal diagnosis (the only couple with an affected fetus chose to terminate the pregnancy).[12 13] Considerable resources will be needed for providing information, counselling, and a national laboratory infrastructure; an economic evaluation of cystic fibrosis screening is in progress (R Beech, personal communication). Carrier screening of the general population seems unrealistic at present, and screening should therefore be offered to selected groups—that is, in the context of reproduction.

General practice and cystic fibrosis screening

What are the likely future developments in screening for cystic fibrosis and how will they affect general practitioners? Data now available indicate that screening should be offered when it is perceived to be directly relevant, both by the person being screened and the primary care worker. The most important times are when patients consult for family planning or preconception advice or when a pregnancy is first reported to the general practitioner. Cascade screening will be particularly relevant in a practice's genetic screening programme. The general practitioner must discuss the importance of family studies with all carriers (including

Practice implications

- A practice of 10 000 patients will contain about 185 cystic fibrosis carriers of reproductive age
- One member of the practice team should be trained to give basic genetic advice
- Testing should be offered when individuals present for family planning or preconception advice or to book a pregnancy
- The offer of testing to relatives of carriers is essential

those identified in antenatal and family planning clinics) and with relatives of affected children.

Confidentiality dictates that partners and other members of a family can be approached only through the person found to be a carrier. This may create problems, as some relatives are likely to be registered with different practices. It will be difficult to offer adequate counselling, both before and after testing, to relatives living in areas without a screening programme. A short video which may be very useful in this situation is available.[14]

Even when appropriate literature is available, explaining genetic concepts is not easy and can be time consuming. Essential pretest information includes a brief description of cystic fibrosis, its inheritance, and implications for child bearing; persuading people that they could be carriers; and explaining that the test fails to identify 15% of carriers. This took on average 10 minutes with two studies, even though individuals were also given a booklet explaining the test.[9,13] With an informed population, counselling would probably take less time.

Post-test counselling of carriers involves reassuring them that they are perfectly healthy; emphasising that the trait is common; and explaining in more detail the inheritance of cystic fibrosis, the reproductive implications of carrying the mutated gene, how the risk can be avoided, and the importance of testing relatives.

While all members of a primary care health team who come into contact with potential parents should be able to give basic genetic information—for example, the rationale for carrier testing—it may be helpful for larger practices to arrange for one member, perhaps a practice nurse, community midwife, or health visitor, to get extra training in basic genetic counselling. He or she will then be able to accept intrapractice referrals of, for example, people who are discovered to be carriers of common inherited disorders. Suitable training courses are available at some regional genetics centres. As we live in a multiethnic community the practice genetic screening programme should include genetic diseases common among ethnic minorities—namely, haemoglobin disorders and Tay-Sachs disease.[15] Other programmes—for example, for carriers of fragile X syndrome—are likely to follow that for cystic fibrosis.

Education

Even targeted screening needs to be accompanied by an information campaign sponsored by the Department of Health and involving the media and relevant voluntary organisations. This should aim at increasing public awareness of cystic fibrosis, its inheritance, and the possibility of prevention. Genetics teaching for teenagers in schools should be focused on conditions possibly relevant to them in the future. Initially health professionals will require further training in view of the large numbers of carriers who will eventually be identified and need counselling. A supply of simply written information to hand out before screening and to give to carriers is essential.

Audit of cystic fibrosis carrier screening

Little information is yet available on how carrier couples without a family history of cystic fibrosis will use the knowledge that they are at risk. We have to extrapolate from experience with couples who already have a child with cystic fibrosis (which indicates that they make considerable use of prenatal diagnosis[16-18]) and from other genetic screening programmes.[19] In Italy and Greece systematic carrier screening and the offer of prenatal diagnosis for thalassaemia major has proved highly acceptable, and the birth incidence of thalassaemic children has fallen dramatically.[20]

There is a danger that the introduction of a cystic fibrosis screening programme could be accompanied by subtle pressure on parents to terminate an affected pregnancy because of the expense of treating people with cystic fibrosis—estimated at about £8000 annually for an adult in 1989.[21] It will be easy to measure changes in the birth rate of children with cystic fibrosis since a patient register already exists (J Dodge, personal communication). A more valid measure of the quality of the service is the number of carrier couples identified in time for them to decide what to do when expecting a child.[22]

Conclusion

The advantages of targeted population screening for carriers of cystic fibrosis outweigh the disadvantages. However, its introduction will need careful preparation. As the population is relatively uninformed,[23] it is difficult to assess whether they wish to be tested or not, but testing is relatively simple, and gradually more people will request it, as with other medical services. In particular, couples with detectable mutations who produce a child with cystic fibrosis are likely to be upset if they have not been offered testing.

As with the early phases of other screening programmes, enthusiastic individuals are initially likely to set up programmes in districts dotted around Britain and in various settings. Antenatal screening is likely to be popular, as it is relatively efficient and the structure for collecting specimens is already in place. Harris *et al* have shown that general practitioners can screen and offer pretest information in the context of reproduction and that this is popular with patients.[13,23] If carrier testing is focused on relevant groups in the practice population then in spite of the recent NHS reforms, which have added considerably to the workload of general practitioners, general practice will be able to accept a central role in cystic fibrosis screening (see box).

Role of general practitioner in cystic fibrosis screening

- Train member of practice team
- Provide information to those offered testing elsewhere
- Offer testing when relevant to life situation
- Counsel single carriers
- Provide cascade screening for relatives of patients and carriers
- Refer carrier couples for genetic counselling
- Support couples after termination of pregnancy

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Grand Rounds—Hammersmith Hospital

Adult moyamoya disease

An unusual cause of stroke

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Moyamoya disease is a cerebrovascular disease of unknown aetiology chiefly reported in the Japanese.[1] It was first described in 1963 and most cases occur in children. Increasing numbers of cases are now being reported in non-Japanese adults, and it is an unusual but important cause of stroke.[2-4] Moyamoya disease commonly manifests with signs and symptoms of cerebral ischaemia or infarction in children, but adults tend to present with intracerebral haemorrhage.[1 5] We report a case of moyamoya in an Indian woman who presented atypically with transient attacks of right sided carpopedal spasm. Subsequently she had a cerebral infarct in the left middle cerebral artery territory—a rare complication of this disease.

Case history

A 43 year old Indian woman presented to the neurological outpatient clinic at Ealing Hospital in February 1992 with a two month history of paroxysmal carpopedal spasm affecting her right hand. The attacks lasted less than five minutes and were sometimes associated with perioral and right hand numbness. Between attacks she had no neurological symptoms. Her symptoms could be induced by hyperventilation and were made worse by hot weather.

Nine days later she developed a severe left sided headache, photophobia, and speech disturbance. She had a severe receptive dysphasia with fluent speech, neologisms, and paraphasic errors. Her right arm had normal power but was severely dyspraxic. She had right visual and somatosensory inattention, dysgraphia, and dyslexia. Funduscopy and cardiovascular examinations gave normal results. Contrast enhanced computed tomography at admission to hospital and seven days later showed a large left temporoparietal infarct in the middle cerebral artery territory. Doppler ultrasonography of the carotids showed dampening of flow in the left internal carotid artery. Echocardiography showed no embolic source. Baseline blood tests, electrocardiography, and chest radiography all gave normal results. A standard screen for young stroke patients including tests for thrombophilia, autoantibodies, and circulating lupus anticoagulant gave negative results.

She partially recovered after speech and occupational therapy and was discharged home 12 days later, having been prescribed 300 mg of soluble aspirin a day. The next day she experienced a transient attack of parasthaesiae and weakness in the right arm and leg. These attacks continued every day. During the attacks she became more dysphasic and afterwards was tired. She did not lose consciousness or have convulsions during the attacks, which could be induced by hyperventilation.

On readmission her neurological status was unchanged except that her right plantar response was now extensor. An electroencephalogram showed increased slow wave activity over the left hemisphere, consistent with the presence of a left sided infarct. Hyperventilation greatly increased the slow wave amplitude, with development of dysphasia and right hemisensory disturbance. Magnetic resonance imaging confirmed the extensive left sided infarct in the middle cerebral artery territory (fig 1), and small foci of high signals were also seen in the left frontal and right peritrigonal areas. High signal lesions were shown on both the T_1 and T_2 weighted images, indicating a combination of haemorrhage and oedema. Non-selective intra-arterial digital subtraction angiography of the extracranial vessels showed a tapering stenosis of the left internal carotid artery with occlusion of the left middle cerebral artery. The appearances were thought to be consistent with a dissection of the left internal carotid artery.

She was given anticoagulating drugs and initially her ischaemic episodes became less frequent. She was discharged with a diagnosis of left frontoparietal infarction due to spontaneous dissection of the left internal carotid artery. However, despite adequate anticoagulation she reported continuing bilateral attacks of carpopedal spasm and numbness at review.

Repeat magnetic resonance imaging showed a more extensive high signal lesion in the left temporal,