The benefits of newborn screening in cystic fibrosis

Cystic fibrosis is a life threatening genetic disease. Those affected are typically at risk of poor nutrition as a result of pancreatic failure and die prematurely from relentless, worsening lung infections. Identifying those who are affected at an early pre-symptomatic stage, affords an opportunity to commence appropriate care in advance of the onset of irreversible complications. This article will review the extent to which newborn screening programmes, such as the one which has recently been rolled out across the whole of the UK, can achieve this.

Gary Connett
Consultant Respiratory Paediatrician
Director of Paediatric Cystic Fibrosis Service
Southampton University Hospitals Trust
conneg@suht.swest.nhs.uk

Keywords

newborn screening; cystic fibrosis; immune reactive trypsin

Key points

Connett G. The benefits of newborn screening in cystic fibrosis. *Infant* 2009; 6(1): 16-18.

1. Positive cystic fibrosis (CF) screening results should be related with care and sensitivity by a healthcare professional who has previously had contact with the family.
2. Arrangements should be made for immediate referral to a specialist CF centre for diagnostic confirmation.
3. Newborn screening provides an opportunity to start CF care early before the onset of disease-related complications that might result in adverse long-term outcomes.

Incidence and diagnosis

Among white caucasians living in the UK, cystic fibrosis (CF) is the most common inherited autosomal recessive disorder with a frequency of around 1 in 2,000 live births. One in 25 of the population are unaffected carriers of a gene for cystic fibrosis. Around the world the incidence varies widely. Whilst common in Arab populations, CF occurs less frequently among peoples originating from India and is very rare among Africans and Orientals. These are important considerations because the ethnic mix of any society will determine the gene frequency of CF gene mutations and the types of CF gene mutations that need to be included in the screening protocols used.

The so-called 'gold standard' diagnostic test for when CF is detected is the sweat test[1]. A weak electrical current, usually applied to the forearm or occasionally the leg in smaller infants, is used to induce sweating with a chemical called pilocarpine (**FIGURE 1**). The sweat is collected either onto clean filter paper or into a coiled capillary tube and the volume and concentration of chloride ions in the sweat is measured. Children with CF have much saltier sweat than the normal population.

FIGURE 1 Sweat test.

In 1989 researchers identified the actual gene that goes wrong in CF. This is called the cystic fibrosis transmembrane conductance regulator (CFTR) and is thought to be primarily involved with the movement of salt and water across various membranes throughout the body[2]. The most common mutation of the CFTR gene in the UK is a base pair deletion called DF508 but over a 1,000 other disease-causing gene mutations have been described worldwide[3].

Screening test

While newborn screening has been available in some parts of the UK for many years, it wasn't until 2007 that a national screening programme was rolled out across the whole of the country. Parents of all newborn infants are offered the option of screening for CF as part of the tests that are performed on heel prick testing, usually towards the end of a baby's first week of life[4]. Those affected are identified as a result of having very high levels of an enzyme called immunoreactive trypsin (IRT) in their blood during this time. Those infants with sustained increases in this enzyme and/or commonly identified mutations of the CF gene on DNA testing are referred on to regional CF centres for sweat test diagnostic confirmation and the early introduction of CF care. In most cases this can be achieved within the first four weeks of life.

Ideally, information about positive screening results should be relayed to the family by an individual who is already

- Improved long term survival
- Better lung function and fewer respiratory complications
- Better nutritional status
- Better cognitive function
- Reduced adverse effects on cases of CF – a low number of 'missed' false negative tests and minimal inappropriate 'labelling' of those with very mild symptoms

TABLE 1 Potential benefits of newborn screening for CF.

known to them. In many cases this is a health visitor although local practices vary. Confirmation of the diagnosis by a specialist CF paediatrician should be arranged as soon as possible. It is good practice for the person relating the diagnosis to come straight to the point, relating simple factual information and without the use of judgemental language. It is important to check what knowledge the family might already have about CF and to give clear positive messages about what can be done next to ensure that the newly diagnosed infant remains healthy. It is a good idea to warn against searching the internet beyond trusted resources such as the Cystic Fibrosis Trust's website.

Screening benefits

Over the last 20 years a number of papers have been written by researchers studying the benefits of early diagnosis in countries where newborn screening has been introduced. **TABLE 1** summarises those aspects of screening that have been examined to determine whether screening is of benefit.

Screening benefits have recently been analysed in a Cochrane review of "Newborn screening for cystic fibrosis"[5]. The main positive findings of this analysis were that screening did result in improved nutritional outcomes and there were also pulmonary benefits during early childhood. However it was difficult to demonstrate long-term benefits. This was largely as a result of confounding effects such as cross infection, that had occurred in some of the large CF centres in North America where the diagnosed babies had been looked after, and unavoidable biases such as pancreatic status in favour of unscreened groups.

Nutritional outcomes

Good nutritional status has been identified over the years as being the most important factor in keeping individuals with CF healthy. The largest study to assess the benefits of screening comes from Wisconsin in North America[6]. The data from this study conclusively showed that the risk of reduced height and the risk of having height and weight below the 10th percentile was significantly reduced in their screened population and that these differences persisted through childhood. Lower vitamin E levels in early childhood were also found among the unscreened group of patients and this was shown to be associated with subsequent reduced levels of cognitive function and verbal skills compared with the CF children identified through screening[7].

Respiratory outcomes

Studies have not shown major benefits from screening in relation to lung function and chest X-ray changes in later childhood. This is probably because of confounding factors such as the acquisition of infection with bacteria such as *Pseudomonas aeruginosa* in the screened group of the Wisconsin study. This is perhaps surprising given that late-diagnosed children often present with persistent chest symptoms as a result of already having developed significant lung complications (see 'Other outcomes' below).

Long-term survival

Life expectancy has increased considerably over recent decades and the vast majority of people with CF can expect to live well into adult life. As a result it is very difficult for studies to show any survival advantage as a result of newborn screening. There is a publication however, from the UK trial evaluating screening, in which two out of seven reported deaths might have been avoided by earlier diagnosis[8].

Other outcomes

One of the difficulties in trying to determine the benefits of screening in population studies is that the data do not take into account the impact of early diagnosis on individual children and their families. Experienced clinicians who have worked in large CF units are unanimous in their opinion that there is a small but important group of patients who come late to diagnosis and have established irreversible bronchiectasis that is likely to have a long-term impact on their future survival. There is no doubt that these complications are avoidable through screening and occur in up to 20% of CF populations in most centres. As a result of modern specialist care these late-diagnosed children can and usually do achieve good health throughout childhood and well into adult life with little effect on respiratory outcomes such as the lung function measure forced expiratory volume in one second (FEV_1). However, there is evidence that the burden of care for these patients in terms of the need for hospital admissions to receive intravenous antibiotics and their daily treatment needs, including the use of nebulised antibiotics, is considerably greater[9]. This has been shown using prospective data comparing early and late diagnosed children identified through the UK CF database.

Late-diagnosed children, with significant symptoms, are likely to have made repeated visits to medical services and to have undergone a lot of investigations into the cause of their symptoms before the diagnosis of CF is finally arrived at. There are also small numbers of children who present with CF in very unusual ways. These include severe anaemia, low protein levels and ascites and unusual metabolic disturbances such as hypochloraemic alkalosis. Such infants are often referred to the wrong specialist services and undergo extensive investigation before a diagnosis of CF is considered. Taking these factors into account there is no doubt that CF screening is highly cost effective.

Psychosocial factors

Clinicians in Leeds have examined the psychosocial aspects of newborn screening for CF[10]. The screening process currently in place in the UK has been shown to be very robust with a very low level of initial 'false positives' for which referral for sweat testing is indicated. As a result, any morbidity within the screened population without CF is very low. The uptake for newborn screening is extremely high with very few parents refusing the heel prick test and there is excellent patient information for families going through the screening process.

One effect of screening is that parents are faced with a life threatening condition in a child who in the majority of cases has yet to experience illness. This is in marked contrast to the pre-screening situation in

which doctors diagnosed CF as a cause of presenting illness during childhood for which treatments were given to relieve symptoms. This has had important implications for the way healthcare professionals now relate the diagnosis of CF to families.

One other important benefit of screening is that couples now have earlier opportunities to make informed reproductive choices about future offspring with CF and can take advantage of genetic counselling and technologies such as antenatal diagnosis and pre-implantation diagnosis.

CF treatment

One of the most important findings from all of the published studies thus far is that whilst screening provides an opportunity for early treatment, the benefits are wholly dependent upon the type of care that the child subsequently receives. The Cystic Fibrosis Trust in the UK and similar organisations in other countries have been very pro-active in facilitating the development and dissemination of evidence-based guidelines for all aspects of care including the specifications for the services that should be met by the specialist multidisciplinary teams working within accredited centres.

Some of the practical aspects of care that are recommended are outlined in **TABLE 2**. Families will need to be taught about all aspects of CF care but the most important early interventions are measures to ensure optimal growth including the use of oral pancreatic enzyme replacements in those who are pancreatic insufficient. This is because of the extremely important relationship between poor nutritional status and worsening lung problems. Growth should be monitored closely through frequent outpatient follow-up visits. These visits will also provide opportunities to collect cough swabs for the early detection of bacterial pathogens in the airways such as *Staphylococcus aureus, Haemophilus influenzae* and *Pseudomonas aeruginosa* for which additional antibiotics will be needed. The families will also need clear advice about starting appropriate additional antibiotics early after the onset of new respiratory symptoms.

- Regular outpatient attendances at least monthly for the first year of life for:
  - Specialist review by the multi-disciplinary CF team
  - Respiratory cultures for CF pathogens
  - Body weight, length and head circumference to ensure optimal growth
- Pancreatic function tests (stool faecal elastase) and early introduction of pancreatic enzyme replacement (pancreatin) in those who are pancreatic insufficient.
- Fat soluble vitamin (A, D and E) replacement therapy where indicated
- Commencement of regular flucloxacillin
- Further investigations including chest X-rays, fibre-optic bronchoscopy and pH studies where indicated.

TABLE 2 Aspects of CF care following diagnosis after newborn screening.

Clear guidelines are also available concerned with practical measures that should be taken within out-patient clinics and on hospital wards to minimise the risks of cross infection between patients with bacteria that have the potential to cause chronic infection and worsening lung damage[11].

Final considerations

The healthcare setting within which the screening programme is provided is also an important factor – countries where there is poor awareness of CF and poor availability of diagnostic testing services are likely to have a lot of late-diagnosed cases *in extremis*. Early diagnosis through screening in this setting is likely to have far greater benefits than screening within a more developed healthcare economy.

Given the current lack of clinical equipoise it is unlikely that there will be future randomised controlled trials to further evaluate the benefits of screening. Further studies should be concerned with refining the screening, diagnostic and subsequent care pathways for newly diagnosed patients to optimise their long-term health. This is all the more important if individuals are to receive maximal benefit from new treatments such as gene therapy and hopes for an eventual cure.

References

1. Guidelines for the performance of the sweat test for the investigation of cystic fibrosis in the UK. http://www.acb.org.uk/docs/sweat.pdf
2. **Kerem B-S., Rommens J.M., Buchanan J.A. et al.** Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989; **245**: 1073-80.
3. **Cystic Fibrosis mutation database.** http://www.genet.sickkids.on.ca/cftr/app
4. **UK Newborn screening programme centre.** http://newbornbloodspot.screening.nhs.uk/professionals
5. **Southern K.W., Mérelle M.M.E., Dankert-Roelse J.E., Nagelkerke A.** Newborn screening for cystic fibrosis. *Cochrane Database Systematic Rev* 2009, Issue 1.
6. **Farrell P.M., Kosorok M.R., Rock M.J. et al.** Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics* 2001; **107**(1): 1-13.
7. **Koscik R.L., Farrell P.M., Kosorok M.R. et al.** Cognitive function of children with cystic fibrosis: deleterious effect of early malnutrition. *Pediatrics* 2004; **113**(6): 1549-45.
8. **Doull I.J., Ryley H.C., Weller P., Goodchild M.C.** Cystic fibrosis-related deaths in infancy and the effect of newborn screening. *Pediatric Pulmonology* 2001; **31**(5): 363-66.
9. **Sims E.J., Clark A., McCormick J., Mehta G., Connett G., Mehta A.** United Kingdom Cystic Fibrosis Database Steering Committee. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics* 2007; **119**(1): 19-28.
10. **Duff A., Brownlee K.** Psychosocial aspects of newborn screening programmes for cystic fibrosis. *Children's Health Care* 2008; **37**: 21-37.
11. **Cystic Fibrosis Trust Consensus Documents.** http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/

Cystic Fibrosis Trust
11 London Road
Bromley
Kent BR11 1BY
Tel: 020 8464 7211
enquiries@cftrust.org.uk
AskTheExpert@cftrust.org.uk
www.cftrust.org.uk