THORAX

Editorials

Neonatal screening for cystic fibrosis

Reliable screening of neonates for cystic fibrosis has been available for about 15 years[1] and it has been used in a number of communities. Soon after its introduction questions were raised about its value and possible adverse effects.[2] In particular, it was suggested that telling parents of an apparently healthy 4–6 week old infant that it had a life-limiting condition may have negative effects on the parent–child interaction.

Several papers have now been published which have evaluated the effects of neonatal screening and in Victoria, Australia, a state with approximately 65 000 births a year, neonatal screening has been undertaken for the last six years. In this issue of *Thorax* (pp 712–718) Dankert-Roelse and te Meerman[3] produce some evidence to indicate that neonatal screening may improve the long term prognosis of the disease. Their study does, however, have some limitations. The screening method used was based on the determination of the albumin content of meconium. This is known to have poor sensitivity as was well demonstrated in that study.[4] The population studied by Dankert-Roelse and te Meerman was born between 1973 and 1979 and may not represent the likely course of cystic fibrosis in children born in 1990s. The survival of their symptomatically diagnosed patients was significantly inferior to that reported at about the same time from elsewhere.[5] The survival of their post-screened population was perhaps more compatible with that expected by a major clinic and was virtually identical to that in their screened population. The median age at diagnosis in their non-screened and post-screened population was substantially higher than that of eight months seen in Victoria, Australia over an equivalent period.[6]

There are no other long term studies of the effects of screening on survival. A study from Melbourne of siblings diagnosed at less than six months by routine sweat tests because of a family history failed to show any long term advantage for this group[7] and there was some similarity to a screened population. With major clinics including our own (Wohlers, Hibbert and Phelan, unpublished data) showing a survival to 15 years of about 80% and to 25 years of at least 50% of patients managed over the last 10 years, it will probably now be very difficult to show any benefit of neonatal screening on long term survival.

Possible benefits

Studies have indicated that infants with cystic fibrosis diagnosed as a result of neonatal screening appear to be better nourished in the first year of life and to have fewer hospital admissions.[8] Both of these findings suggest that there could be long term advantages. As a result of logistic and ethical problems there are virtually no long term studies of appropriate outcome measures, such as lung function, in groups from the same community diagnosed either as a result of screening or of symptoms over a similar time period and managed by the same physicians.

The experience in Victoria, Australia

Those involved in neonatal screening and in the management of cystic fibrosis in Melbourne were unenthusiastic about screening of neonates for cystic fibrosis. However, for several reasons not directly related to a conviction that it would make a major difference to the outcome of the disease, it was introduced in March 1989. From that date until February 1995 95 infants have been diagnosed as a result of neonatal screening, 25 as a result of presentation with meconium ileus, and 17 born after March 1989 as a result of presentation with either chronic respiratory or gastrointestinal symptoms. Of these, 11 were missed in the serum immunoreactive trypsin screen and six had no delta F508 mutation. There were 28 terminations for cystic fibrosis in that period.

While detailed studies of the attitudes of families to their infants have not been undertaken, there have been minimal difficulties observed by the clinical personnel. Very careful consideration was given to the way the diagnosis of cystic fibrosis was presented to the families and only five physicians have been involved over that period. They have all adopted a similar positive, though honest, approach to the implications of the diagnosis of cystic fibrosis. Almost all families have accepted the diagnosis and, in fact, many had already observed some abnormal symptoms in their infant as had been noted by others.[9] We have continued our practice of admitting all newly diagnosed infants to hospital for a period of investigation and parent education, irrespective of the presence of symptoms or not, and this may well have helped parents to come to terms with the diagnosis. We currently use a Care by Parent Unit attached to the Royal Children's Hospital and this has been of particular value.

There has, however, been one major benefit from the neonatal screening programme. Before its introduction many parents had been anxious for months, or even years, about their child and had attended many doctors to seek an explanation for the chronic respiratory symptoms, poor growth, or abnormal stool function without a diagnosis being established. This led to much anger and frustration and often made the establishment of a good therapeutic relationship difficult.[10] We no longer see these problems. The elimination of these months of anxiety for many families has been of major importance. Family attitude is of crucial importance in the management of chronic illness in children, and being able to help to foster a very positive attitude from the time of diagnosis may well have a major influence on long term outcome. Our impression is that

families now much more readily accept their child as a normal subject with a health problem that can be controlled with optimal treatment than as a chronically ill child who needs to be protected. The families tend to embrace enthusiastically advice about the importance of good nutrition and a very active lifestyle.

Therefore, from being a group which was initially doubtful about the introduction of neonatal screening, we have now become enthusiasts for it. We believe it has improved the overall wellbeing of our patients with cystic fibrosis and their families even though it may not be possible – even in the long term – to demonstrate that it alters ultimate survival. It is recognised that this conclusion is based on impression and will be almost impossible to prove scientifically. Controlled trials of such factors as parental attitudes are extremely difficult.

Screening process

When screening was originally introduced in Victoria the two stage serum immunoreactive trypsin method was used.[1] This involved the measurement of serum levels of immunoreactive trypsin (IRT) in the blood spot already collected from all newborn infants at day 4 for the detection of phenylketonuria and hypothyroidism. Infants with the highest 0·7% of serum IRT levels were recalled for a second measurement. If the level remained high they were asked to attend for sweat testing. Of those who underwent a sweat test about 25% had cystic fibrosis. This meant that in a population of 100 000 neonates 700 required a second measurement of serum IRT and approximately 150 a sweat test. Much anxiety was generated among the false positive cases during the first and second measurements of serum IRT levels.

In 1991 a one state measurement of serum IRT levels followed by DNA analysis for the commonest cystic fibrosis mutation in this community (delta F508) in those infants from the top 0·7 percentile was introduced[11] and has eliminated most of the false positives. Now, from a population of 100 000 approximately 20 infants will be homozygous for delta F508 mutations and another 40 or so will have raised serum IRT levels and be heterozygous for the delta F508 mutation. These cases are called in for a sweat test and 15–18 will be positive. The parents of the infants who are heterozygous for the delta F508 mutation and have a normal sweat test can then be appropriately counselled and reassured. No long term studies have been done on this group but it is probably important to do so to ensure that the parents do not have any long term anxieties. However, the number at risk of problems is now very much smaller than when a two stage serum IRT measurement was used for neonatal screening.

Should neonatal screening be recommended?

Whether a community introduces neonatal screening for cystic fibrosis or not must depend on its health priorities. The cost is not insignificant – in Victoria it is about US$5000 for each infant identified solely by neonatal screening. As indicated, the main benefit seems to be the reduction in the substantial period of anxiety for parents between the development of symptoms of cystic fibrosis and the ultimate establishment of a diagnosis. Communities in which there is normally a prolonged delay may find the introduction of neonatal screening of even more value in altering long term outcome because the risk of the development of irreversible lung disease before diagnosis may be reduced.

However, neonatal screening should only be introduced if there is a very clear process available to inform the patients promptly and to refer them to a specialised clinic whose staff are skilled in the presentation of the diagnosis to families who have not yet become unduly concerned about the health of their infant.

In the longer term there may be new treatments for cystic fibrosis that will be of more value if instituted soon after birth, but in 1995 no such treatment is available nor is it likely to be available in the near future.

Conclusion

Neonatal screening for cystic fibrosis does not have such clearly defined benefits as that for phenylketonuria and hypothyroidism. It is of value, however, but in each community a true cost-benefit analysis should be carried out before it is introduced. On its own it will not result in a dramatic change to the outlook for patients with cystic fibrosis. Of much greater importance is the existence of specialist multidisciplinary teams for the management of children, adolescents, and adults with this chronic life limiting condition.

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