NEWBORN SCREENING FOR CYSTIC FIBROSIS. EFFICACY/ EFFECTIVENESS AND IMPLEMENTATION PROTOCOLS.

Spanish full text

ABSTRACT

Introduction: Cystic fibrosis (CF) is the most frequent severe autosomal recessive genetic disorder among the Caucasian population, with an incidence in Spain of 1/2810-3743 newborns (27-36/100000). It is a systemic disorder that mainly affects lung and pancreatic function, with a high morbidity and mortality. Life expectancy has risen in recent decades thanks to improved disease management, though there is still no curative treatment. Over 1900 CFTR gene mutations (gene for the protein CF transmembrane conductance regulator) have been detected but not all would appear to cause the disease. The most common severe mutation world-wide is ΔF508. The availability of screening tests, such as immunoreactive trypsinogen (IRT) determination and CFTR gene-mutation-detection panels, have led to generalised implementation of newborn screening programmes for this disease.

Objectives

1. To assess the efficacy/effectiveness and safety of newborn CF screening.
2. To describe the various newborn CF screening strategies (screening protocols; screening test; diagnostic test; outcome assessment; referral units/centres; screening-programme quality assurance).

Methods

We conducted a systematic review of the scientific literature to:

1. assess the **efficacy/effectiveness and safety** of newborn CF screening, with the updated report issued by the Galician Health Technology Assessment Agency (avalia-t) in 2004; and
2. compile information on the implementation of newborn CF screening programmes.

Using pre-established inclusion and exclusion criteria, our search methodology targeted all main databases. The process was completed by a general search of the official web pages of all newborn screening programmes implemented at a national or international level.

Results and discussion

1. **Efficacy/effectiveness and safety of newborn CF screening.** A total of 4 systematic reviews and 4 observational studies were included. The available scientific evidence, based on studies of good methodological quality, indicated that early treatment yielded benefits in the nutritional status and, hence, the growth of newborns identified by newborn screening with respect to those who were clinically diagnosed. No clear benefit in pulmonary involvement was observed, however. Although observational studies indicated a certain benefit in terms of lung function, the methodological quality of such studies was not high. The adverse effects of screening (false positive results, false negative results, borderline diagnosis and detection of healthy carriers) depended on the screening strategy used. The economic evaluation data showed that the cost of the screening programme was lower than that of conventional clinical diagnosis.

2. **Implementation of a newborn CF screening programme.** Twenty data sources were selected. Newborn CF screening programmes had no standardised protocol, with the algorithms used displaying a high degree of inter-country and even inter-regional heterogeneity. The initial screening test consisted of determining IRT levels in a heel blood sample taken from the newborn. There was no standard cut-off point for the purpose of defining positive results. The following stages of the strategy for screening for positive results were very varied and might entail:

   1) repeating the IRT determination in a second blood sample taken at 14-21 days of life (IRT/IRT);

   2) performing a genetic test on the initial blood spot sample, to identify CFTR gene mutations (IRT/DNA); and/or

   3) determining pancreatitis associated protein (PAP) levels in an initial blood sample (IRT/PAP).

   These stages differed from one programme to another, not only in terms of the cut-off points established, but also in terms of the possible combinations of such stages. The strategy chosen inevitably influenced the ultimate sensitivity and specificity of the CF screening: in general, good results were reported, with values of 70%-100% for sensitivity and 99.4-99.9 for specificity. The CF diagnostic test is well established and consists of quantifying the concentration of chloride in sweat.

Conclusions

- Current scientific evidence indicates that early treatment yields benefits in the anthropometric development and nutritional status of newborns identified by newborn screening as compared to clinically diagnosed children. No clear benefit has been seen in the progress of pulmonary involvement.

- The screening protocol is complex, since a positive result in the initial screening test requires complementary screening tests to be performed and there is no standardised strategy. CF screening protocols depend on the specific context of each programme. Furthermore, the choice of any

given protocol will depend on the programme's capacity to assume the burden of the complementary tests proposed.

- While the initial test is common to all newborn screening programmes and consists of determining IRT levels in a heel blood sample taken during the first days of life, there is no standard cut-off point. The subsequent stages differ according to the individual programmes, and can consist of a second IRT determination, PAP determination, or performance of a genetic test to detect CFTR gene mutations. The number of mutations detected will depend on the commercial kit or DNA analysis technique used.

- Parents must be properly informed of the benefits and harm of the screening programme, and in the case of strategies in which genetic tests are used, consideration must be given to other ethical and legal aspects, such as the obligatory need for informed written consent and proper genetic counselling about carrier status.

- The CF diagnostic confirmation test is the sweat test. Accurate diagnosis of CF is achieved where chloride levels exceed 60mmol/l, with CF being ruled out where such levels are under 30mmol/l. Intermediate sweat test values (30-60mmol/l) are classified as borderline results and call for special assessment and management.

- Owing to the complexity of the disease, all newborns diagnosed with cystic fibrosis should be referred for proper management and follow-up to referral centres, which must in turn be provided with the necessary multidisciplinary teams and appropriate facilities for delivering fully-integrated health care, as well as the capability to treat and offer advice on CF-related complications.

Recommendations

- Current scientific evidence shows that newborn CF screening is a diagnostic advance on the absence of screening and yields a clear benefit in terms of growth and nutritional status. Accordingly, newborn CF screening should be included in neonatal metabolic disorder screening programmes in the respective Spanish Autonomous Regions.

- Prior to implementing a newborn CF screening programme, an action protocol must be drawn up with a detailed list of the guidelines to be followed for each of its stages (information to be given to parents; screening tests; diagnostic test; management and follow-up protocol for those children who are diagnosed; genetic counselling for parents, relatives and carriers; and quality assurance of the entire screening process).

- The proposed CF screening test is the heel blood sample routinely taken on the 2nd to 5th day of life, in strict accordance with the specific quality protocols in every case.

- Bearing in mind that the most widely used strategy in Spanish-based newborn screening programmes is that of a single extraction of blood, IRT determination in the heel blood sample can be included as the first stage, followed by a genetic test that would include the most common CFTR gene mutations in the same blood sample (IRT/DNA).

- The choice of the CFRT gene-mutation panel should be based on the mutations' frequency of appearance in the population targeted by the programme and their potential to cause the disease. All mutations registering a frequency of appearance of 0.5 or higher should be screened.

- In the event of failure to obtain consent for undertaking genetic analysis, one alternative might be to draw up a protocol for analytical determination of IRT in a second blood specimen (IRT/IRT) or determination of PAP (IRT/PAP) in the initial blood sample.

- The initial IRT cut-off point must be defined in line with sensitivity and specificity as defined by the programme.

- All newborns with a positive result in the screening process must undergo the diagnostic sweat test, which is recommended even if two CFTR gene mutations are detected in the genetic analysis.

- Newborn CF screening programmes must guarantee equitable and universal access for all newborns (100% coverage) as well as protection of confidentiality. Follow-up should be conducted at referral units that ensure fully integrated treatment of CF, as a fundamental requirement for effectively fulfilling the programme's goals and achieving the greatest benefits possible.

- Prior to implementing newborn CF screening, steps should be taken to ensure that all the ethical and legal aspects are reviewed by a health-care ethics committee. Should the programme envisage research work, this must also be authorised by a research ethics committee.