Cystic Fibrosis Newborn Screening in a Portuguese Centre: Are we Complying with European Recommendations?

Rastreio Neonatal de Fibrose Quística num Centro de Referência: Estaremos a Cumprir com as Recomendações Europeias?

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Dear editor,

It has been nearly 40 years since the first newborn screening (NBS) program for cystic fibrosis (CF) was implemented.[1] In Portugal the screening was introduced in October 2013 as a pilot study, being fully integrated in the national program for early diagnosis in December 2018. It implies a dried blood sample between the third and sixth day of age, where an immunoreactive trypsin (IRT) value is obtained. If IRT is over 65 mg/dL, the level of pancreatitis-associated protein (PAP) is obtained. If PAP level is higher than 1.6 mg/dL, a second dried blood sample is obtained, between the third and fourth weeks of age. If the second IRT level is higher than 50 mg/dL, the infant is CF NBS-positive and is referred to a CF centre for sweat chloride test (SCT) and genetic testing, if deemed adequate.[2-4] CF is diagnosed when, in an infant with suggestive symptoms, or a family history of CF, or a positive NBS for CF, two SCT > 60 mmol/L are obtained and/or two disease-causing CF mutations are detected through DNA analysis.[5]

We retrospectively analysed the data on children with positive NBS for CF assessed at our centre between October 2013 and December 2021, then calculated the rate of false positives, false negatives, the positive predictive value, and sensitivity of the programme, in our population.

During this time, 54 infants were referred from the NBS program. Among these, 22 (40%) were confirmed to have CF through SCT. Two infants were also diagnosed with CF, despite a negative NBS. Patients' characteristics are described in Table 1.

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Table 1. Clinical features and laboratory findings of infants with a positive screening and a CF diagnosis

	Positive screening + CF diagnosis (n=22)
Diagnostic age (day), median (IQR)	32.8 (21.2 - 38)
Age at first evaluation (day), median (IQR)	38.5 (22.7 – 40.2)
Sweat Test (mean, mEq/L) median (IQR)	83.05 (73.75-90)
Pancreatic insufficiency, n (%)	20 (90.9)
Genetic analysis	
At least one *F508del* mutation, n (%)	20 (90.9)
Homozygous for *F508del* mutations, n (%)	11 (50)
First evaluation	
Birth weight (gr), median (IQR)	3035 (2455 - 3265)
Steatorrhea, n (%)	16 (72.7)
Insufficient weight gain, n (%)	9 (40.9)
Reluctance to feeding, n (%)	2 (9)
Irritability, n (%)	2 (9)
Respiratory symptoms, n (%)	5 (22.7)
Microbiology	
Age at first sputum sample collection (day), median (IQR)	43.5 (40 – 61.7)
Bacteria identified in first sputum sample, n (%)	14 (63.6)
Pseudomonas aeruginosa, n (%)	3 (13.6)
Escherichia coli, n (%)	6 (27)
Staphylococcus aureus, n (%)	6 (27)

Fourteen infants were male (63%), the mean age at diagnosis was 33 days (min. 11, max. 83) and the mean age at the first evaluation in a CF centre was 38.5 days (min. 17, max. 110). Eleven (50%) infants were homozygous for *F508del|p.Phe508del* mutation and 91% had at least one *F508del|p.Phe508del* mutation. The mean SCT level was 83.05 mmol/L (IQR 73,75 - 90), 91% of the infants were pancreatic insufficient at presentation and 63% had bacterial growth in sputum samples at first evaluation.

The sensitivity of the screening program in our population was 91% and the positive predictive value (PPV) was 40%. The rate of false negatives was 8% and false positives 60%.

The European Cystic Fibrosis Society (ECFS) recommends that NBS programmes should aim for a minimum PPV of 30%, a minimum sensitivity of 95%. [5] Previous reports showed that countries have different strategies regarding the NBS program, and only 62% of the countries met the recommended PPV and 69% the recommended sensitivity. [6]

In our study, the program showed a sensitivity of 91%. However, these results represent only one of the five Portuguese CF centres. Furthermore, the sample was small, with only 22 infants with CF and 2 infants with a negative screening that were later diagnosed with CF. Both infants had less common *CFTR* mutations (one was homozygous for Y569D|p.Tyr569Asp, the other heterozygous *F508del|p.Phe508del / L206W|p.Leu-206Trp*) and additionally the second one was pancreatic sufficient at diagnosis.

The ECFS also recommends that CF NBS-positive infants should be observed in a CF centre by 35 days after birth, on average, and never more than 58 days.[5] Our infants were observed for the first time at our centre at 38.5 days of age.

Countries must reflect critically on their NBS programmes, so they can be optimized, and become as efficient as possible. This can only be done through quality monitoring, reassessment, and dialogue between those responsible. This local retrospective assessment demonstrated good program performance locally, however, further studies are needed to verify if the recommendations are met at a national level.

Awards and previous presentations

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BC: Bibliographical search, study design, data collection, drafting of the article

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BC: Pesquisa bibliográfica, delineamento do estudo, colheita de dados, redação do artigo

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