The first five-year evaluation of cystic fibrosis neonatal screening program in São Paulo State, Brazil

Uma avaliação dos primeiros cinco anos do programa de triagem neonatal da fibrose cística no Estado de São Paulo, Brasil

Una evaluación de los primeros cinco años del programa de cribado neonatal de fibrosis cística en el Estado de São Paulo, Brasil

Abstract

The Hospital of the Ribeirão Preto Medical School, University of São Paulo is one of the three screening centers in São Paulo State, Brazil, and has included a test for cystic fibrosis (CF) since February 6, 2010, by a court order. We evaluated the first five years of this CF-newborn screening program. The original immunoreactive trypsinogen (IRT)/IRT screening protocol was adopted in Brazil. A total of 173,571 newborns were screened, 1,922 (1.1%) of whom showed IRT1 $\geq$ 70ng/mL. Of these, 1,795 (93.4%) collected IRT2, with elevated results (IRT2 $\geq$ 70ng/mL) in 102 of them (5.2%). We identified a total of 26 CF cases during this period, including three CF cases that were not detected by the CF-newborn screening. The incidence of the disease among the screened babies was 1:6,675 newborns screened. Median age at the initial evaluation was 42 days, comparable to that of neonates screened with the IRT/DNA protocol. Almost all infants with CF already exhibited some manifestations of the disease during the neonatal period. The mutation most frequently detected in the CF cases was F508del. These findings suggest the early age at the beginning of treatment at our center was due to the effort of the persons involved in the program regarding an effective active search. Considering the false negative results of CF-newborn screening and the early onset of clinical manifestations of the disease in this study, pediatricians should be aware of the diagnosis of CF even in children with negative test.

Cystic Fibrosis; Neonatal Screening; Trypsinogen

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Introduction

Cystic fibrosis (CF) is a hereditary autosomal recessive disease with an incidence ranging from 1:2,000 to 1:10,000 among Caucasians in several countries. In Brazil, its incidence has been estimated at 1:7,576 to 1:8,400 live births. CF is associated with changes in the ion transport regulatory transmembrane protein (CFTR – cystic fibrosis transmbrane regulatory), which, among other functions, acts as a chloride channel that carries this ion out of the cell. More than 2,000 mutations in the CFTR gene have already been described and, depending on the mutation, the protein defect may be more or less severe, with consequent differences in the clinical presentation of the disease or in the patient’s age at the onset of the disease.

Newborn screening for CF (CF-NBS) became available in 1979 and in recent years has been expanded around the world.

Immunoreactive trypsinogen (IRT) determination is the starting point for NBS in all protocols used thus far although IRT levels can be elevated in various situations not related to CF. The original IRT/IRT screening protocol was adopted in Brazil in view of the ethnic heterogeneity of the Brazilian population and the need to investigate various mutations, despite the known large number of false-positive results which induce unnecessary anxiety in the parents until the diagnosis of CF can be ruled out.

In Brazil, CF-NBS has been performed in some states (Paraná, Santa Catarina and Minas Gerais) since 2001, but in São Paulo State it began only on February 6, 2010. Currently, the entire country has introduced CF-NBS.

In São Paulo State, there are three neonatal screening centers: Hospital of the Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), University of Campinas (UNICAMP) and Association of Parents and Friends of the Exceptional (APAE) of São Paulo. NBS Program of HCFMRP-USP covers the screening of children born in the northeastern region of São Paulo State.

The objectives of this study are to report the data regarding CF-NBS at HCFMRP-USP and to perform a critical analysis of the results of this screening five years after its implementation.

Patients and methods

We analyzed retrospectively the results of all newborns whose NBS tests were sent to HCFMRP-USP from February 6, 2010 to January 31, 2015, and the clinical and laboratory data of all babies whose screening was positive for the disease and who were therefore evaluated at the Cystic Fibrosis Outpatient Clinic of HCFMRP-USP. We also included babies with a negative CF-NBS, but with a CF diagnosis confirmed by clinical signs and symptoms suggestive of the disease and a positive sweat chloride test (SCT). For data collection, we used the database of the Neonatal Screening Laboratory of HCFMRP-USP, the records of the hospital system and clinical records of the children diagnosed with CF.

The strategy used for CF-NBS was the IRT/IRT protocol, which recommends a first collection of the test (IRT1) between the third and fifth day of life and a second IRT collection (IRT2) between three and four weeks of life for children with IRT1 results ≥ 70ng/mL. If the IRT2 value remained high (≥ 70ng/mL), the children were re-called for clinical evaluation and the SCT was performed for diagnostic confirmation. Collections were considered to be late when IRT1 was collected at more than 15 days of age, a situation in which IRT1 was considered to be IRT2, or when IRT1 or IRT2 was collected after more than 30 or 45 days, respectively.

Blood samples were collected on Schleicher & Schuell # 903 filter paper at the hospitals and basic health care units of the cities and sent to the Screening Laboratory of HCFMRP-USP. IRT was measured with the commercial DELFIA Neonatal IRT kit (time-resolved fluoroimmunoassay kit A005-110, Wallac Oy, USA) using immunofluorimetric methodology according to the manufacturer’s guidelines. The intra-assay coefficient of variation was 5.9% at the concentration of 20.0ng/mL and the inter-assay error was 6.7% at the concentration of 26.4ng/mL. The method used in the SCT is based on the stimulation of pilocarpine sweating and iontophoresis in the
forearm and subsequent determination of chloride in sweat-soaked gauze by spectrophotometry using the modified commercial kit (Labtest Diagnostica S.A., Brazil).

Chloride concentrations in the sweat test below 30mEq/L were considered normal and concentrations higher than 60mEq/L were considered to represent a diagnosis of CF. Intermediate values between 30 and 60mEq/L were considered to be doubtful, and the test was repeated on another day.

The results of NBS tests were considered to be false positive in the presence of two results of IRT ≥ 70ng/mL followed by a normal SCT and to be false negative when the child had one or two normal IRTs, and the diagnosis of CF was performed based on clinical manifestations of the disease and two positive SCT.

Clinical evaluation of babies with IRT1 and IRT2 ≥ 70ng/mL was performed by a pediatric gastroenterology specialist after the SCT. All children diagnosed with CF and those with a SCT in the doubtful range were referred to the CF Outpatient Clinic for follow-up.

Clinical manifestations of the patients diagnosed with CF were collected at the first consultation in the specialized clinic and were subdivided as follows: gastrointestinal in the presence of steatorrhea, vomiting or diarrhea; respiratory in the presence of persistent coughing, wheezing or repetitive “pneumonia”, and/or “metabolic” in the presence of dehydration or lack of weight gain.

The variables studied were: median age (interquartile range – IQR) of the child at collection of the first IRT, positivity in the NSB test and in the SCT, sensitivity and specificity of the NBS test, time of CF diagnosis and initial clinical manifestations of babies with a diagnosis of CF. Babies with meconium ileus were excluded from the determination of sensitivity. The dates of each NBS step were analyzed in order to determine the effectiveness of the CF-NBS Program.

DNA amplification and molecular analysis

- **Sanger sequencing assay**

Eighteen patients (Table 1) were subjected to sequencing of the entire CFTR coding region. Genomic DNA was extracted from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit (Promega, Madison, USA) according to the manufacturer’s instructions. Thirty-two pairs of primers were designed to amplify the 27 exons and adjacent intronic regions of the CFTR gene (primer sequences and PCR conditions available upon request). The PCR-amplified DNA fragments were subjected to direct sequencing with an automatic capillary sequencing system (ABI 3500X Genetic Analyzer, Applied Biosystems, Foster City, USA) using the Big Dye terminator v3.1 cycle sequencing kit (Applied Biosystems) and the same PCR primers, following the manufacturer’s instructions. Results were analyzed using the FinchTV software, version 1.4.0 (https://digitalworldbiology.com/FinchTV) and the sequences obtained were compared to the reference of the GenBank database (NM_000492).

- **Multiplex Ligation-dependent Probe Amplification (MLPA) assay**

Patients bearing none or heterozygous for CFTR deleterious mutations were submitted to MLPA for the screening of deletions or duplications in CFTR gene. We employed the SALSA MLPA P091-CFTR kit (MRC-Holland), according to manufacturer’s instructions. Results were analyzed using the software Coffalyser for MLPA data interpretation.

**Results**

From February 2010 to January 2015, 176,562 births occurred according to the Brazilian Information System on Live Births (SINASC) and 173,571 newborn were subjected to the NBS test at HCFMRP-USP. The median age (IQR) at test collection (IRT1) was 5.0 (4-7) days. Of the total number of children screened, 1,946 (1.1%) presented IRT1 ≥ 70 ng/mL. Of these, 1,795 (93.4%) collected IRT2, with a result ≥ 70ng/mL in 102 of them (5.7%) (Figure 1). The median [IQR] age for the collection of IRT2 was 28 (24-33) days.
Table 1
Clinical and laboratory data of newborns with cystic fibrosis detected at Hospital of the Ribeirão Preto Medical School, University of São Paulo, from February 2010 to January 2015.

| Newborn | Gestational age (weeks) | IRT1 (ng/mL) | IRT2 (ng/mL) | Sweat chlorine (mEq/L) | Onset of symptoms (day) | Clinical manifestations | Age at 1st evaluation (day) |
|---------|-------------------------|--------------|--------------|------------------------|-------------------------|------------------------|--------------------------|
| 1       | 39                      | 145.0        | 73.9         | 94.8                   | 15                      | Yes                    | 30                       |
| 2       | 37                      | 83.4         | 89.2         | 83.0                   | Birth                   | Yes                    | 53                       |
| 3       | 38                      | 205.0        | 90.5         | 53.5                   | Birth                   | Yes                    | 93                       |
| 4       | 36                      | 140.0        | 93.7         | 112.6                  | Birth                   | Yes                    | 48                       |
| 5       | 40                      | 71.6         | 101.0        | 59.5                   | Birth                   | Yes                    | 35                       |
| 6       | 38                      | 105.0        | 116.0        | 69.7                   | Birth                   | Yes                    | 41                       |
| 7       | 39                      | 203.0        | 152.0        | 138.0                  | Birth                   | Yes                    | 35                       |
| 8       | 38                      | 156.0        | 153.0        | 98.7                   | Birth                   | Yes                    | 35                       |
| 9       | 39                      | 194.0        | 165.0        | 70.9                   | Birth                   | MI                     | 1                        |
| 10      | 33                      | 154.0        | 172.0        | 126.3                  | Birth                   | MI                     | 1                        |
| 11      | 37                      | 251.0        | 191.0        | 197.0                  | Birth                   | MI                     | 1                        |
| 12      | 38                      | 303.0        | 226.0        | 131.1                  | 15                      | Yes                    | 53                       |
| 13      | 38                      | 485.0        | 232.0        | 88.8                   | Birth                   | Yes                    | 31                       |
| 14      | 40                      | 139.0        | 272.0        | 75.0                   | Birth                   | Yes                    | 43                       |
| 15      | 35                      | 317.0        | 295.0        | 170.0                  | Birth                   | Yes                    | 49                       |
| 16      | 35                      | 187.0        | NC           | 110.0                  | Birth                   | Yes                    | 97                       |
| 17      | 39                      | 83.4         | LC           | 55.9                   | 40                      | Yes                    | 82                       |
| 18      | 38                      | 166.0        | NC           | 65.1                   | Birth                   | Yes                    | 51                       |
| 19      | 40                      | 119.0        | NC           | 53.7                   | Birth                   | Yes                    | 90                       |
| 20      | 38                      | 204.0        | 124.0        | 115.2                  | Birth                   | Yes                    | 34                       |
| 21      | 38                      | 143.0        | 120.0        | 52.1                   | 30                      | Yes                    | 34                       |
| 22 *    | 39                      | 298.0        | 189.0        | 59.7                   | 23                      | Yes                    | 25                       |
| 23 *    | 26                      | 77.0         | 74.2         | ND                     | Birth                   | MI                     | 33                       |
| 24 **   | 40                      | 39.0         | -            | 88.3                   | 60                      | Yes                    | 118                      |
| 25 **   | 39                      | 48.5         | -            | 126.5                  | 60                      | Yes                    | 264                      |
| 26 **   | 37                      | 92.9         | 54.8         | 63                     | 60                      | Yes                    | 475                      |

IRT: immunoreactive trypsinogen; LC: late collection; MI: meconium ileus; NC: not collected; ND: not done.
* Death;
** False negative.

The SCT was performed in 90 (88.2%) of the babies with elevated IRT2 and 63 (61.8%) had normal results (Figure 1). Fifteen children had a SCT ≥ 60mEq/L: the diagnosis of CF was confirmed in all but one, with the latter being considered a false positive NBS test. The SCT of 12 babies was ≥ 30 and < 60mEq/L: CF was confirmed in four; seven of them were considered be false-positive NBS results and one NB died at three months of age.

Among the babies with IRT2 ≥ 70ng/mL, two were not subjected to the SCT due to loss of follow-up and ten died. One of the children who died had a diagnosis of meconium ileus at birth, and therefore a diagnosis of CF (Figure 1).

A total of 119 babies (6.2%) were not subjected to the IRT2 (Figure 2): 23 died and ten were not located due to a change of address. Eighty-six NB were located and called for the SCT because they were older than one month. Among these children, the SCT was elevated in three, and CF was confirmed.

Thirty-two children had late IRT1 or IRT2 collections (Figure 3): ten died, one was lost to follow-up and 21 performed the SCT, which was positive in only one of them.
Figure 1

Results of immunoreactive trypsinogen (IRT)/IRT screening strategy.

Figure 2

Results of cystic fibrosis screening strategy in children who did not harvest immunoreactive trypsinogen (IRT2).

Figure 3

Results of cystic fibrosis screening strategy in children who had late collection of samples.
Forty-four deaths (2.3%) occurred among the babies subjected to IRT1 collection during the study period (n = 1,946), one of them with meconium ileus and another with an elevated SCT who had actually started treatment with pancreatin but who died in her hometown and was not submitted to autopsy. Most of the babies who died had complex congenital cardiopathies, renal malformations, and genetic syndromes. Few of these babies’ autopsy reports were obtained since most deaths occurred in their hometowns and autopsies are often not authorized by the parents in Brazil.

During the study period, three babies with a negative NBS test (false-negative result) were detected as having CF. The results of their SCTs were 63, 88.3 and 126.5mEq/L and their age at diagnosis was 475, 264 and 118 days, respectively.

Considering all the cases detected (n = 26) during the study period, one affected patient per 6,675 screened newborn was identified. Median age (IQR) at IRT2 collection was 26 (21.5-30.2) days and median age at the SCT was 44 days (34.5-59). Among the babies with an elevated IRT2 (n = 102), the result was false positive in 71 of them (69.6%). The sensitivity of the NBS test using the IRT/IRT protocol for CF was 88.5%, specificity was 98.9%, the positive predictive value was 1.2%, the negative predictive values was 99.9%, and accuracy was 97.9%.

The median age (IQR) at first evaluation was 42 (32-73) days for all babies detected by screening and 43 (35-81) days with the exclusion of four babies with meconium ileus (Table 1).

Almost all babies with CF already exhibited some clinical manifestations during the neonatal period, mainly gastrointestinal symptoms (17/26, 65.4%) with four of them having meconium ileus, pulmonary symptoms (12/26, 46.1%) and metabolic symptoms (9/26, 34.6%). The complete patient characteristics for IRT, SCTs, and CFTR genotype are described in Tables 1 and 2.

| Newborn | Sanger sequencing | MLPA                     |
|---------|-------------------|--------------------------|
| 1       | Positive for the F508del mutation in homozygosis in exon 11 in the CFTR gene | ND                       |
| 2       | Positive for the F508del and Leu997Phe mutations in heterozygosis in exons 11 and 19, respectively in the CFTR gene | ND                       |
| 3       | Positive for the Met470Val mutation in homozygosis and F508del in heterozygosis, both in exon 11 in the CFTR gene | No deletions/No duplications |
| 4       | Positive for the Gly85Glu and F508del mutations in heterozygosis in exons 3 and 11, respectively, in the CFTR gene | F508del in heterozygosis |
| 5       | Positive for the F508del mutation in homozygosis in exon 11 in the CFTR gene | F508del in homozygosis |
| 6       | Positive for the Pro205Ser mutation in exon 6 of the CFTR gene and for the pathogenic allele 5T/TG12 in the IVS8 region in the CFTR gene | No deletions/No duplications |
| 7       | Positive for the Met470Val mutation in homozygosis in exon 11 and for Arg1162Stop in heterozygosis in exon 22 in the CFTR gene | No deletions/No duplications |
| 8       | Positive for the F508del mutation in homozygosis in exon 11 in the CFTR gene | F508del in homozygosis |
| 9       | Positive for the F508del mutation in homozygosis in exon 11 in the CFTR gene | ND                       |
| 10      | ND                 | ND                       |
| 11      | ND                 | ND                       |
| 12      | Positive for the F508del mutation in heterozygosis in exon 11 in the CFTR gene | F508del in heterozygosis |
| 13      | Positive for the Gly85Glu and F508del mutations in heterozygosis in exons 3 and 11, respectively, in the CFTR gene | F508del in heterozygosis |
| 14      | Positive for the Met470Val mutation in homozygosis in exon 11 in the CFTR gene | No deletions/No duplications |
| 15      | Positive for the F508del mutation in homozygosis in exon 11 in the CFTR gene | ND                       |
| 16      | Negative for mutations in the coding region of the CFTR gene | Exon 2 deletion in heterozygosis |

(continues)
Table 2 (continued)

| Newborn | Sanger sequencing | MLPA |
|---------|-------------------|------|
| 17      | Positive for the Ala349Pro mutations in exon 8 of the CFTR gene and for the pathogenic allele ST/TG12 in the IVS8 region in the CFTR gene | No deletions/No duplications |
| 18      | Positive for the mutations I148N in exon 4 and Jle507del in exon 11, both in heterozygosis, in the CFTR gene | ND |
| 19      | Positive for the Leu206Trp and F508del mutations in heterozygosis in exons 6 and 11, respectively, in the CFTR gene | F508del in heterozygosis |
| 20      | ND                 | ND   |
| 21      | Positive for mutations Arg117His e Gly542Stop in heterozygosis in exons 4 and 12, respectively, in the CFTR gene | ND   |
| 22 *    | ND                 | ND   |
| 23 *    | ND                 | ND   |
| 24 **   | ND                 | ND   |
| 25 **   | ND                 | ND   |
| 26 **   | ND                 | ND   |

CFTR: cystic fibrosis transmembrane regulatory; MLPA: Multiplex Ligation-dependent Probe Amplification assay; ND: not done.

* Death; ** False negative.

Discussion

During the study period, 176,562 births occurred according to the System of Information about Liveborns (SINASC) and 173,571 NB were screened at HCFMRP-USP, demonstrating excellent program coverage (98.3%). IRT2 was collected in 93.4% of the babies and the frequency of IRT2 positivity was 5.3% among those with an elevated IRT1 and 0.6% considering the total number of babies screened. The screening test showed 88.5% sensitivity, but a high 98.9% specificity. The positive predictive value was 1.2%, demonstrating that one of the negative factors about neonatal screening was that 1,899 families of supposedly healthy babies needed to live with the expectation of their children having CF, with a reduction to 102 families during the period between IRT2 and the SCT. The median age of affected babies at the time of the SCT was 42 days and the median age at first evaluation was 43 days, which was a positive factor both for an early release of babies without a diagnosis of CF and for an early intervention in babies with the disease.

The original IRT/IRT screening protocol was adopted in Brazil in view of the ethnic heterogeneity of its population. In the US, the IRT/IRT protocol is used in only 10% of NBs and its use is declining due to its low sensitivity, delayed diagnosis and high rate of false-positive results compared to the IRT/DNA protocol, which also promotes the identification of CF heterozygote carrier families for genetic counseling. However, the use of DNA analysis has several potential disadvantages like the recognition of babies with misidentified paternity. A variation of the IRT/DNA method, called IRT/IRT/DNA, has been suggested, which requires the demonstration of persistent hypertrypsinoegenemia for 1-2 weeks before DNA analysis. Although the time to diagnosis may be longer than in the IRT/DNA programs, IRT/IRT/DNA screening is more sensitive and detects fewer carriers.

Sanders et al., 2012, compared ages at diagnosis, genotyping, SCT, and first visit to a CF Center between US states that used serial IRT/IRT levels and states that used IRT/DNA analysis. In states using IRT/DNA, the babies were younger at the time of diagnosis (median 2.3 weeks versus 4.0 weeks, \( p < 0.001 \)) or genotyping (0.7 weeks versus 5.3 weeks, \( p < 0.001 \)), and the initial visit to the CF center occurred earlier (5.9 weeks versus 7.7 weeks, \( p = 0.008 \)). At our center, the median age of affected babies at the first evaluation was 42 days and 43 days when excluding the babies with meconium ileus. Among the diagnosed cases, three did not harvest the IRT2 and one of them had the late collection (Figures 2 and 3). The diagnosis was made by the SCT performed at 51, 82, 90, and 97 days of life.
The early age at the beginning of treatment at our center reflects the effort of the persons involved in the program so that, even though using the IRT/IRT protocol and despite the fact that a large number of babies did not perform the IRT2 or had a late collection. The SCT was performed in a timely manner for the babies to receive an early diagnosis and treatment comparable to those for the babies who were screened by the IRT/DNA protocol in the study by Sanders et al. 20.

Three babies had the CF diagnosis despite a negative NBS test. The diagnosis was made on a clinical basis and the interval until the beginning of treatment for these babies was longer compared to that of the other screened children, i.e., 118, 264, and 475 days of life under quite precarious health conditions. A delayed diagnosis of CF due to a previously negative NBS test indicates the need for further information including CF in the differential diagnosis of some diseases regardless of the NBS test 21. Fritz & Farell 21 estimated 70 cases of false-negative results among 4,038,560 babies screened per year in the US using the IRT/DNA or IRT/IRT protocol. Thus, clinical and laboratory signs and symptoms suggestive of CF should not be ignored since a delayed diagnosis may have serious or even lethal consequences.

The frequency of CF in the present population was one in 6,675 screened newborns, a slightly higher value than that reported in a pilot study at this same center (1:8,403) involving a smaller number of babies and those reported for other Brazilian states (Paraná 1:9,520, Santa Catarina 1:8,776; Minas Gerais: 1:9,115) 22,23,24.

Most of the babies with CF already showed some clinical manifestations at diagnosis (Table 1), although none of them had been diagnosed previously. The lack of a diagnosis even in the presence of clinical manifestations underscores the importance of the test for the population involved since the mean age at diagnosis is higher without NBS.

Improved nutrition was the primary benefit of CF-NBS identified in the randomized controlled trial conducted by Farrell et al. 25 and continues to be the most significant outcome of an early diagnosis 26. Tluczek et al. 27 reported no difference in pulmonary function or quality of life outcomes between screening and control patients when controlling for pancreatic function and Pseudomonas aeruginosa infection. However, other studies indicate a protective benefit of CF-NBS for nutritional status and pulmonary function as well as reduced complications 28,29.

Previously considered lethal in infancy and childhood, CF has now permitted a median survival of 50 years of age in affected patients, mainly thanks to an early diagnosis through NBS, recognition of mild forms, and an aggressive therapeutic attitude.

Most of the affected babies studied here were subjected to a genetic study and the mutation most frequently detected was that most commonly encountered in all populations, i.e., F508del, which is detected in approximately 70% of CF cases around the world 30.

Therefore, due to the heterogeneity of clinical features already described in CF, it becomes important to include the screening for mutations in the CFTR gene in the CF-NBS. Thus, the majority of suspected cases of CF would be detected early, favoring early treatment and management of the disease.

In conclusion, the incidence of CF among the screened babies was 1:6,675. The median age at IRT1 collection of the babies with altered results was five days. Because of an active search, most babies (93.4%) came for IRT2 collection at a median age of 26 days, a time that will need to be reduced in order to obtain an earlier diagnosis. The median age at the first evaluation for babies with confirmed diagnosis, excluding those with meconium ileus, was 43 days. Neonatal screening permitted the beginning of treatment at an earlier age, although most babies already showed some clinical manifestations of the disease. Considering the false negative results of CF-NBS and the early onset of clinical manifestations of the disease in this study, pediatricians should be aware of the diagnosis of CF even in children with negative test.
Contributors

All authors contributed in the conception and design, acquisition of data, analysis and drafting of the manuscript.

Additional informations

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Resumo

O Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo é um dos três centros de triagem da fibrose cística (FC) no estado de São Paulo, tendo incluído esse teste desde 6 de fevereiro de 2010, a partir de uma liminar judicial. O estudo avalia os primeiros cinco anos desse programa de triagem neonatal da FC. O Brasil adota o protocolo de triagem original, com o tripsinogênio imunorreativo (IRT)/IRT. Foram triados um total de 173.571 recém-nascidos, dos quais 1.922 (1,1%) mostraram IRT≥70ng/mL. Destes, 1.795 (93,4%) tiveram amostras coletadas para IRT2, com resultados elevados (IRT2≥70ng/mL) em 102 deles (5,2%). Identificamos um total de 26 casos de FC durante esse período, inclusive 3 casos de FC que não foram detectados com a triagem neonatal. A incidência da FC foi de 1 caso em cada 6.675 recém-nascidos triados. A idade mediana na avaliação inicial foi 42 dias, comparável à idade de recém-nascidos triados com o protocolo IRT/DNA. Quase todos os lactentes com FC já exibiam algumas manifestações da doença durante o período neonatal. A mutação mais comum nos casos de FC foi a F508del. Os resultados em nosso centro indicam que a idade precoce no início do tratamento foi devido aos esforços do programa na implementação de uma busca ativa eficaz. Considerando os resultados falsos-negativos no programa de triagem neonatal para FC e o início precoce das manifestações clínicas da doença neste estudo, os pediatras devem estar cientes da possibilidade de diagnóstico de FC, mesmo em crianças com teste negativo.

Fibrose Cística; Triagem Neonatal; Tripsinogênio

Resumen

El Hospital das Clínicas de la Facultad de Medicina de Ribeirão Preto, Sao Paulo Universidad es uno de los tres centros de cribado de fibrosis cística (FC) en el estado de Sao Paulo, incluyendo este test desde el 6 de febrero de 2010, debido a una medida cautelar judicial. El estudio evalúa los primeros cinco años de este programa de cribado neonatal de FC. Brasil adopta el protocolo de cribado original, con el tripsinógeno inmunorreactivo (TIR)/IRT. Se cribaron un total de 173.571 recién nacidos, de los cuales 1.922 (1,1%) mostraron IRT≥70ng/mL. De estos, se obtuvieron 1.795 (93,4%) muestras recogidas para IRT2, con resultados elevados (IRT2≥70ng/mL) en 102 de ellos (5,2%). Identificamos un total de 26 casos de FC durante ese periodo, inclusive 3 casos de FC que no fueron detectados con el cribado neonatal. La incidencia de la FC fue de 1 caso por cada 6.675 recién nacidos cribados. La edad media en la evaluación inicial fue 42 días, comparable a la edad de recién nacidos cribados con el protocolo IRT/DNA. Casi todos los lactantes con FC ya manifestaban algunos síntomas de la enfermedad durante el período neonatal. La mutación más común en los casos de FC era el F508del. Los resultados en nuestro centro indican que la edad precoz en el inicio del tratamiento se debía a los esfuerzos del programa en la implementación de una búsqueda activa eficaz. Considerando los resultados falsos-negativos en el programa de cribado neonatal para FC, y el inicio precoz de las manifestaciones clínicas de la enfermedad en este estudio, los pediatras deben ser conscientes de la posibilidad de diagnóstico de FC, incluso en niños con test negativo.

Fibrosis Quística; Tamizaje Neonatal; Tripsinógeno

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