Preliminary results of the pilot study for Cystic Fibrosis newborn screening in Portugal

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INTRODUCTION

Cystic Fibrosis (CF, MIM 219700) is the most common lethal genetic disorder among Caucasians (1: 3 000). It's an autosomal recessive disease, caused by mutations in the CFTR gene, and its diagnosis is frequently delayed due to the non-specificity of a wide variety of clinical symptoms, including chronic lung disease, pancreatic dysfunction, elevated chloride levels in sweat and male infertility. The elevation of immunoreactive trypsinogen (IRT) in the blood of CF newborns makes feasible the newborn screening (NBS) for this disease (Crossley et al., 1979), but IRT is a low specificity marker.

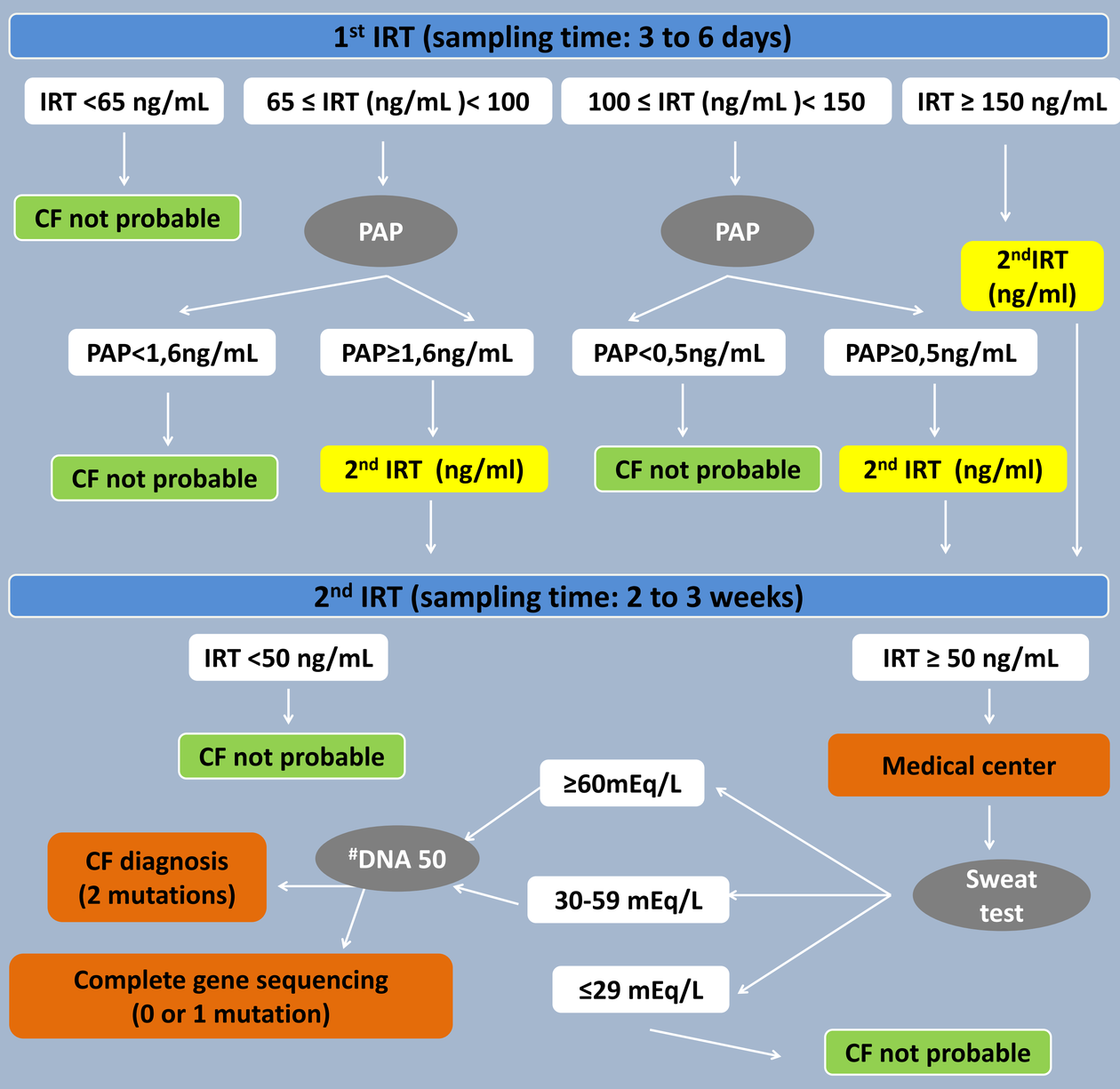
Pancreatitis-associated protein (PAP) was also demonstrated to have elevated concentrations in CF newborns (Sarles et al., 1999) and several strategies including IRT as 1st marker and PAP or genetic analysis as 2nd or 3rd tier tests, are still being tested and implemented in different countries. Although the advantages of CF NBS are considered clear, and most newborns in North America, Australasia and Europe are already being screened for CF, there's yet no agreement regarding the best strategy to use.

In October 2013, a pilot study for CF NBS in 80 000 newborns was started, which intents to determine the best strategy for the Portuguese population.

PATIENTS AND METHODS

An IRT/PAP/IRT strategy is being used (Figure 1) and 52 000 newborns were already screened.

Figure 1 - Portuguese strategy for CF NBS



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RESULTS

From the 52 000 newborns screened, 485 (0.93%) presented an increased IRT level. In 35 of these cases, IRT was higher than 150 ng/mL and a 2nd sample was immediately requested.

PAP determination was done for 450 newborns, from which 192 cases had increased levels, according to Figure 1. From the 227 second samples (0.37% recall rate), eleven presented persistent elevated IRT levels and these newborns were sent to a specialized medical center for further evaluation (Table 1).

In 2 cases (Table 1, cases 10 and 11) the sweat test revealed to be negative.

Nine patients (Table 1, cases 1 to 9) were confirmed though positive sweat test or genetic analysis.

All nine patients identified have at least one F508del allele and seven of them were homozygotes for this mutation.

Table 1 – Newborns sent to specialized medical center

Cases nº (sampling days)	1st IRT (N<65ng/mL)	PAP*	2nd IRT (N<50ng/mL)	Genotype
1 (5d, 18d)	94	5,4	158	F508del/F508del
2 (21d, --)	129	3,9	n.d.	F508del/F508del
3 (6d, 14d)	210	>8,8	287	F508del/?
4 (23d, 28d)	190	>8,8	195	F508del/F508del
5 (3d, 13d)	260	4,3	344	F508del/F508del
6 (4d, 27d)	266	>8,8	360	F508del/F508del
7 (5d, 15d)	443	>8,8	480	F508del/F508del
8 (4d, -----)	202	2,7	n.d.	F508del/N1303K
9 (2d, 5d)	101	>8,8	85	F508del/F508del
10 (4d, 24d)	65	2,8	56	n.d.
11 (4d, 18d)	68	2,3	67	n.d.

*N<0,5ng/mL if IRT ≥100 ng/mL or N<1,6ng/mL if IRT< 100ng/mL

DISCUSSION AND CONCLUSIONS

PAP determination, in combination with IRT determination, allowed us to considerably reduce the number of 2nd samples requisition (from 0.93% to 0.37%), and seems to be a valuable approach in the CF NBS strategy.

According with these results, F508del mutation seems to be much frequent in our population than previously thought, which may indicate that a genetic approach based on F508del detection could also be interesting in our population.

CF seems to have in Portugal a 1: 5 700 approximate frequency.