

Inconclusive Cystic Fibrosis neonatal screening results: long-term psychosocial effects on parents

Sandra Perobelli, PhD
Clinical psychologist
Cystic Fibrosis Center
Azienda Ospedaliera-Universitaria
Verona (Italy)

Baroukh Maurice Assael, MD
Head
Cystic Fibrosis Center
Azienda Ospedaliera-Universitaria
Verona (Italy)

Carlo Castellani, MD
Co-ordinator CF Neonatal Screening
Cystic Fibrosis Center
Azienda Ospedaliera-Universitaria
Verona (Italy)

INTRODUCTION

Although Cystic Fibrosis neonatal screening aims at identifying newborns with undisputable Cystic Fibrosis (CF), it may occasionally detect infants where a CF diagnosis can neither be confirmed nor excluded.

These babies usually show, together with high immunoreactive trypsinogen (IRT) values, borderline or even normal sweat chloride levels, and their genotype may include *CFTR* mutations of unclear clinical meaning.

These infants are possibly affected by a *CFTR*-related disorder, i.e. a clinical entity associated with *CFTR* mutations, but where a diagnosis of CF cannot be made by the current standard diagnostic criteria (1,2). The long-term phenotypical consequences may be highly variable and some of these children might over time develop CF, others could never have any symptoms (3–6).

Such variability makes it impossible to predict the individual clinical outcome (7,8). Parents of newborns with “ambiguous diagnosis” (AD) are given the message that, although their children are now healthy, there could be long-term consequences, which are impossible to predict, and are offered clinical follow-up. This prognostic uncertainty may potentially cause considerable distress in the family.

This study was aimed at assessing emotional reactions of families in which CF neonatal screening led to such ambiguous situation and parents' attitude toward the medical system.

Populations under study

Three groups of parents were investigated: group AD, Cystic Fibrosis Diagnosis (CFD) and Healthy Controls (HC). Group AD comprised the parents of all infants who met the following inclusion criteria: born in the period from January 1997 through December 2004, IRT levels at birth above the neonatal screening cut-off, two *CFTR* mutations of which only one acknowledged to be CF-causing, sweat chloride values between 30 and 60 mmol/L. All told, 11 families were invited (11 mothers, 11 fathers); all agreed to participate. During the 1997–2004 time period, 367 960 newborns were screened for CF in Veneto and Trentino Alto-Adige regions (Italy). Group CFD included mothers and fathers of 11 children diagnosed with CF through neonatal screening, all of them regularly attending the Verona CF Centre. All these children had elevated sweat chloride values, clearly consistent with CF. All were matched with group AD children by age and gender. Group HC included mothers and fathers of 11 healthy children, negative to CF neonatal screening, and matched with group AD and CFD children by age and gender. They were recruited by paediatric practitioners among children seen

for standard health supervision visits.

CF newborn screening procedure

Immunoreactive trypsinogen levels are measured in dried blood spot specimens from all the neonates born in the Veneto and Trentino Alto-Adige regions (Italy) since the early 1980s. Since 1993, mutation analysis is performed and meconium lactase tested in all whose IRT concentration is above a 99.5 centile cut-off. Diagnosis is immediately established in newborns either homozygous or compound heterozygous for two CF-causing mutations, who are referred directly for a confirmative sweat test and clinical management. Since 1997, neonates whose sweat chloride is in the intermediate range (30–60 mmol/L) undergo a CFTR gene scanning of all 27 exons and intronic flanking regions with denaturing gradient gel electrophoresis, and if necessary sequencing. If this analysis detects a CFTR sequence variation whose clinical consequences are unclear or highly variable, the infants are monitored in the Verona CF Centre every 6–12 months with clinical evaluations, repeated sweat testing and use of ancillary tests like chest X-rays, faecal chymotrypsin and respiratory tract cultures.

During the peripartum period, parents are provided with information about CF neonatal screening by the maternity unit staff. Verbal information is supplemented by specifically designed brochures. The positive results of the neonatal screening procedure and its implications are always communicated to both parents by the same CF Centre physician. The main concepts delivered to families of infants with CF include information on CF inheritance mechanisms, a clinical description of the disease, principles of treatment and follow-up and, given the clinical heterogeneity of CF and the poor genotype/phenotype correlation, the impossibility at this stage of an individualized prognosis. The main concepts delivered to families of infants with inconclusive results include a clinical description of CF, and highlight how it is impossible to predict the clinical outcome of the newborn. It is stressed that at present, the baby is healthy and that over time he/she could maintain good health, or, if male, manifest conditions like congenital bilateral absence of the vas deferens or develop other manifestations like pancreatitis, sinusitis and chest disease. It is also explained that it can not be excluded that some cases may end up having CF.

Questionnaire

A structured questionnaire was designed based upon (i) key psychological themes identified in the literature on psychosocial consequences of neonatal screening (9-12), (ii) pilot interviews between some CF/AD families and the CF Centre psychologist and (iii) information obtained through focus-discussions among CF team members (physicians, nurses, psychologist, social worker). The final questionnaire contained 25 items, consisting of three sections. The questionnaire included a mixture of open-ended and multiple-choice questions, 0–5/0–10 visual analogical scales questions, and extra space for comments as well as separate fields for mothers' and fathers' answers.

The 1st section investigated circumstances of diagnosis and parents' emotional reaction.

The 2nd section, completed also by a control group of parents of healthy children matched for sex and age, investigated how the child's health is perceived in the family.

The 3rd section investigated the impact of diagnosis on the parents' emotive status, on the couple relationship and on the parent-child relationship.

Comparison of AD versus CFD group on rating scale items was made by Wilcoxon matched-pairs signed ranks test.

MAIN RESULTS

- The reaction to the communication of neonatal screening results was intense in mothers of both newborns with AD and with CF, but significantly much so in the latter.

	Group AD Mean–median (range)	Group CF Mean–median (range)	p values
<i>“What level of anxiety did the communication of the sweat test result cause you?*</i>			
In the mother	8.9-10 (5-10)	9.6-10 (8-10)	0.04
In the father	7.9-9 (4-10)	9.3-10 (6-10)	0.02
In the parents	8.4-10 (4-10)	9.5-10 (6-10)	0.003

*scale: 0-10= 'none at all'-a high level'

- Contrary to parents of children with CF, in the first months of life, parents and family members of babies with inconclusive neonatal screening results do not differ from control parents of healthy children in terms of health perception. Over time CF parents develop a better perception of the children's health. The perception of their children's health is anyway significantly better in group AD than in group CFD, when parents compare their CF children with healthy peers.

	Group AD Mean–median (range)	Group CFD Mean–median (range)	Group HC Mean–median (range)	p-values
<i>‘In the first months of life, our child's health was...’*</i>	1.8–2 (1–3)	2.7–2 (1–4)	2.4–3 (1–4)	AD/HC: ns AD/CFD: 0.01
<i>‘During the last year, our child's health has been...’*</i>	1.9–2 (1–4)	2.4–2 (1–4)	1.9–2 (1–3)	ns
<i>‘In comparison with peers, his/her health was...’</i>	2.1-2 (1-3)	3.1-3 (2-4)	2.5-3 (1-4)	AD/HC: N.S. AD/CFD: 0.03

*scale: 1 = 'very good'; 2 = 'good'; 3 = 'average'; 4 = 'poor'; 5 = 'very poor'

- Levels of anxiety concerning the child's health are in general lower in parents of infants with AD than in parents of children with CF. Nevertheless, the similar levels of emotional disturbances reported by parents of the two groups suggest that inconclusive neonatal screening results are anyway stressful.

	Group AD Mean–median (range)	Group CFD Mean–median (range)	Group HC Mean–median (range)	p-values
<i>“Your child's health is for you cause of anxiety? ”*</i>	3.1-3 (2-5)	4-4 (3-5)	2.4-3 (1-4)	AD/HC: ns AD/CFD: 0.01
<i>‘Do you believe you suffer from emotional disturbances connected with your child's health?’</i>	n. “Yes”	n. “Yes”	n. “Yes”	
In mothers and fathers	13	20	2	AD/HC: 0.0003 AD/CFD: n.s

*scale 0-5= 'minimal' – 'extreme'



- Regarding the parent/child relationship, parents of group AD have reportedly been less influenced by diagnosis than those of group CFD. Parents of CF children report that they tend to be excessively protective and indulgent with their children, and acknowledge that such attitude may be wrong.

	Group AD Mean–median (range)	Group CFD Mean–median (range)	p-values
<i>'How much has this diagnosis influenced your relationship with your child?....'</i> [*] In mothers and fathers	0.8-0 (0-8)	3.6-4 (0-10)	AD/HC: ns AD/CFD: 0.01

^{*}scale 0-10= 'not at all' – 'very much'

- Parents reported that their relationships and family planning were influenced in a similar way in the groups. The baby with CF or AD was the first child for six AD and five CFD couples. In group AD, only one couple had another child, with no prenatal diagnosis. In group CFD, two couples had three further pregnancies, and for all pregnancies, prenatal diagnosis was requested: one pregnancy resulted in spontaneous abortion before the chorionic villus sampling, one in termination following a positive prenatal diagnosis and one in the birth of a heterozygous sibling.

	Group AD (n.)	Group CFD (n.)	p-values
<i>'Do you feel that this diagnosis has influenced your couple relationship?'</i>			
<i>'It hasn't been influenced'</i>	8	5	ns
<i>'It has improved'</i>	1	2	
<i>'It has deteriorated'</i>	1	4	

- Most parents in both groups evaluated positively the health services, considered CF neonatal screening useful and conveyed the genetic information to their relatives.

	Group AD Mean–median (range)	Group CFD Mean–median (range)	p-values
<i>'How useful was the diagnosis for your child's development?'</i> ^{**}	3.8-4 (3-4)	3.8-4 (3-4)	ns
<i>'Have you informed your relatives of the availability of the carrier test?'</i>	n. "Yes" 10	n. "Yes" 11	ns
<i>'As a consequence of this experience, how has your opinion of the health services changed?'</i>			
<i>'it has improved'</i>	6	5	ns
<i>'no change'</i>	3	4	
<i>'it has worsened'</i>	1	2	

^{**}scale 1-4: 'totally useless' – 'very useful'

CONCLUSION

Our experience shows that parents of children whose CF neonatal screening results were inconclusive results, and who were offered adequate communication and clinical follow-up, understood properly the information received. They also had a correct perception of their children's health status, which they considered not different from their peers'. However parents reported a greater degree of emotional disturbances related to their children's health than healthy control and similar to parents of CF children diagnosed by neonatal screening.

There is a general agreement that exhaustive and coherent information is crucial to minimize emotional distress connected with CF neonatal screening potential side effects (9,11,13). In the study area, the procedures involving communication of neonatal screening results and clinical follow-up are centralized and managed by a small number of specialized professionals. The consistency in the information provided both at diagnosis and in later years has possibly fostered a better acceptance of the 'AD'.

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