Psychological Effects of False-Positive Results in Cystic Fibrosis Newborn Screening: A Two-Year Follow-Up

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Objective To evaluate parental stress after a false-positive result at the time of the cystic fibrosis (CF) newborn screening (NBS), attributable to heterozygotism or persistent hypertrypsinemia.
Study design A prospective study was conducted in 86 French families at 3, 12, and 24 months after NBS. A psychologist conducted interviews with a questionnaire, the Perceived Stress Scale, and the Vulnerable Child Scale.
Results Overall, 96.5% of parents said they had been anxious at the time of the sweat test. However, 86% felt entirely reassured 3 months after the test. The mean Perceived Stress Scale score did not differ from that observed in the French population. Mean Vulnerable Child Scale scores were high, associated with a low Parental Perception of Child Vulnerability. These results did not differ significantly at 1 and 2 years. In total, 86% to 100% of families no longer worried about CF. All parents stated that they would have the test performed again for another child.
Conclusions CF NBS can lead to false-positive results, causing parental anxiety, which quickly decreases after a sweat test performed soon after the phone call. *(J Pediatr 2010;156:771-6)*.

In 2002, a French nationwide cystic fibrosis (CF) newborn screening (NBS) program was implemented to ensure early diagnosis and optimal treatment in specialized CF centers (CRCM). This screening was based on a blood sample measurement[1] of immunoreactive trypsin (IRT) levels combined with other NBS tests performed 3 days after birth.

The measurement of IRT levels was based on 2 analytical techniques, radioimmunologic assay and immunofluorometry.[2] When results were higher than the thresholds, a search for CF gene mutations was performed in addition to the IRT measurement. This search addressed 30 CF transmembrane conductance regulator (CFTR) gene mutations (Kit Elucigen CF 30 Orchid ARMS PCR amplification; Tepnel diagnostics, Oxon, United Kingdom),[2] representing 90% of the mutations observed in France. Parental consent was obtained *a priori* on the collection of the blood spots 3 days after birth.[2]

When a mutation was identified, the newborn was referred to the CRCM for a sweat test. Two situations were possible when a single mutation was observed: 1) The newborn was a carrier of a second mutation not identified with the screening test, and in this case, the sweat test results would be abnormal; or 2) the newborn was simply heterozygous (HZ), and in this case, the sweat test results would be normal, and genetic counseling was offered to the parents. In the absence of any mutation, another IRT test was performed on day 21 after birth, but to avoid a high number of false-positive results, this test was only administered to children with very high IRT levels on day 3 after birth ($\geq$100 μg/L). When the result on day 21 after birth was above the threshold level, the CRCM conducted a sweat test.[2]

As with most mass screening programs, the CF NBS test produces false-positive results and an acceptable number of false-negative results, estimated at 0.1% and 3.4%, respectively.[2] The primary objective of this study was to evaluate the manner in which parents were affected in the long-term when they were informed of a possible positive CF diagnosis, which later was revealed to be a false-positive result.

Methods

This was a prospective, multicenter, observational study without direct benefits, conducted in 11 French CF Centers (Angers, Grenoble, Lille, Nancy, Nantes,

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CRCM	Specialized cystic fibrosis centers
HZ	Heterozygous
IRT	Immunoreactive trypsin
NBS	Newborn screening
PHT	Persistent hypertrypsinemia
PPCV	Parental Perception of Child Vulnerability
PSS	Perceived Stress Score
VCS	Vulnerable Child Scale

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Rennes, Roscoff, Toulouse, Tours, Vannes, and Versailles) with the approval of a French ethics committee.

All the children with a normal CF sweat test results (chloride concentration <30mmol/L) were admitted to the CRCM between July 2004 and June 2006 to be included in the study. This resulted in 2 distinct groups. After the IRT test conducted on day 21 after birth, the first group had persistent hypertrypsinemia (PHT), with no mutation identified in the most frequent CFTR gene mutations. The second group was HZ, with only 1 CFTR gene mutation identified. Children with CF or with any other neonatal pathology were excluded from the study.

Organization of the Study

The doctor at the regional NBS program or at the CRCM informed parents of the abnormal IRT result on the telephone. It was imperative that the first meeting take place the same day as the call, or the next day at the latest, to not prolong the parents' anxiety. The phone call was standardized, the words "cystic fibrosis" were never used, and families were informed that additional investigations would be needed because of technical problems.

A sweat test was conducted according to the Gibson and Cooke method[3] or with Exsudose (Exsudose system, TEM, Lormont, France). In the HZ group, all the test results were confirmed with the Gibson and Cooke method. In the PHT group, no confirmation with the Gibson and Cooke method was necessary when the examination results were normal. The results were communicated to the families within the hour. Preferably, both parents were present during the consultation.

In the case of normal sweat test results, parents were asked for their consent to participate in the study. After 3 months, 1 year, and 2 years, families were questioned at home by a CRCM psychologist using a pre-established questionnaire. Data from these sessions was recorded anonymously with identification numbers known only by the study investigators. Only 1 response was taken into account, most often that of the mother. The same psychologist conducted the 3 interviews, with the exception of 3 centers.

Evaluation Criteria and Collection of Data

The evaluation criteria were the Perceived Stress Scale (PSS) and the Vulnerable Child Scale (VCS) scores. The PPS was designed in 1988 by Cohen et al[4] and is based on 14 items. Scores range from 0 to 56. A higher score reflects higher perceived stress levels. This scale has an excellent internal consistency (Cronbach's α = 0.84-0.86). The average score for French male subjects was 20.2 ($\pm$ 6.9 SD), and for French female subjects, the average score was 20.9 ($\pm$6.7 SD).[5]

The VCS of Perrin and Culley[6] is based on Green and Solnit's hypothesis,[7] according to which a child is perceived by his parents as being significantly more vulnerable in the long term when he has been exposed to an acute event threatening his health. This scale correlates with the Parental Perception of Child Vulnerability (PPCV). A lower VCS score reflects a higher parental perception of child vulnerability, and thus a higher PPCV. However, VCS has no pathological threshold. The VCS comprises 15 items, rated 1 to 4, with a good internal consistency (Cronbach's α = 0.73).[8]

The residual anxiety evaluation was based on these scales and the results of a questionnaire. In the questionnaire, parents were asked whether they felt totally reassured about CF and whether they had considered CF when the child was ill. However, in the HZ group, residual anxiety was only evaluated with a questionnaire.

After excluding patients lost to follow-up, responses at 3, 12, and 24 months were compared within each family to judge the evolution of their anxiety.

Statistical Analysis

In the 2 groups of independent individuals, quantitative variables were compared by using the Student *t* test or the Wilcoxon-Mann-Whitney test (for n <30), and qualitative variables were compared by using the χ^2 test or Fisher exact test (for n <5). In 2 paired series, the quantitative variables were compared by using the Student paired *t* test or the Wilcoxon rank test (for n <30), and qualitative variables were compared by using the McNemar χ^2 test. In several paired series (>2), quantitative variables were compared with the Friedman test. For all the tests, a *P* value <.05 was considered to be significant.

Results

Regardless of whether the centers recruited >10 children or <10 children and irrespective of the parents' level of education, results at 3 months, 1 year, and 2 years did not differ significantly.

Three Months

A total of 86 patients were included in the study, of which 62 were in the HZ group (61 mothers and 1 father) and 24 (all mothers) were in the PHT group. Data were collected at 3 months, 1 year, and 2 years from the same parent. The 2 groups were comparable in age (HZ group, 30.8 $\pm$ 0.8 versus PHT group, 31.1 $\pm$ 1.1), socioprofessional category, and number of children (56% versus 64% had no other children, 22% versus 18% had 1 other child, 19% versus 18% had 2 other children, and 3% versus 0% had 3 other children for the HZ and PHT groups, respectively).

Recall Concerning the Sweat Test

Three months after the sweat test, parents recalled that they had expressed significant anxiety about this examination (Table I). With a single exception, all parents confirmed that they had been informed about the test, but only 67% of the PHT group understood the information that had been presented to them. The information about the sweat test was not standardized.

Residual Anxiety

Residual anxiety was evaluated by using a standardized questionnaire and 2 scales, the PSS and the VCS. At 3 months, the entire PHT group and 83% of the HZ group no longer