

## ETHICAL ISSUES IN CYSTIC FIBROSIS

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### ABSTRACT

In recent decades, the rapid advances in the diagnosis and treatment of cystic fibrosis led to the emergence of ethical issues related to neonatal screening, gene therapy, organ transplantation, and fertility. Also, transition of patients with cystic fibrosis from pediatric to adult care is not only a professional but also an ethical issue. Understanding the ethical issues related to this condition is crucial to providing optimal care.

**Keywords:** cystic fibrosis, ethical, screening, gene therapy, transplants, fertility

### INTRODUCTION

Understanding the ethical issues in cystic fibrosis (CF) is an essential component of providing optimal care. Newborn screening is an important public health prevention program. Over time, the criteria that must be met and the related ethical issues have generated significant controversy. Gene therapy, that offers great promise for patients with CF, must also comply with the basic ethical principles applicable to other therapies. Advances in assisted reproductive technology and lung transplantation remain ethically problematic. Transition from pediatric to adult care is not only a professional but also an ethical issue.

### NEONATAL SCREENING FOR CF

Cystic fibrosis is a condition that complies with the WHO criteria for newborn screening application. The first European experience in newborn CF screening dates back in the early 1970s with programs examining the albumin content of meconium. Later, in 1979, the measurement of immunoreactive trypsin (IRT) in dried blood spots collected from newborns was initiated (1). Informing families both before and after neonatal screening is very

important. Before screening, information is intended to help parents understand the benefits and limitations of this test, being essential for obtaining parental informed consent. Recommendations for pre-screening communication should include the following key messages:

- screening is a test recommended for all newborns;
- the main purpose of screening is to identify cases that require early intervention to improve future development;
- test is safe, harmless to the newborn;
- some infants may require retesting;
- parents should only receive essential information in a simple and concise format (1,2).

After screening, the communication of a positive result is a critical time both medically and psychologically. The time lag between the communication of screening result and confirmatory tests is a period of uncertainty, which should be minimized. The choosing of words used in conversation is important, and the bad news should be preceded by words of encouragement. After obtaining a positive results, parents should be informed in person. If this is not possible, communication by letter or telephone should be very careful to avoid misun-

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derstanding and prevent psychological problems. We will attract attention that a positive screening test result is not confirmation of a diagnosis of CF, further tests being needed to confirm or exclude the disease. Both parents should be informed at the same about the diagnosis of CF. If only one parent can be present, then he/she should be accompanied by a relative or friend. After communicating the diagnosis of CF, the first consultation with parents should focus on the relationship between parents and the team that monitors the child (1,3,4). Some ethicists suggest the routine communication of normal screening results, while some parents do not want to be informed unless there is a problem (5).

Newborn screening for CF has many benefits: early detection has positive effects on growth; prevention of morbidity due to deficits in protein and fat soluble vitamins; better lung function and a 2-3 times reduction in the number of hospitalizations as compared with those diagnosed clinically; genetic counseling; allows a better understanding of the natural history and pathophysiology of the disease (6).

But screening also presents some hazards: false-positive values may cause parental anxiety; false-negative values may lead to a delay in diagnosis; reporting of carriers may be unwanted information and may cause discrimination; errors may occur in communicating or understanding the results; the test has a high sensitivity, but its low specificity requires second-line investigations to confirm the diagnosis of CF (6).

## CF AND GENE THERAPY

Still in the experimental stage, gene therapy is increasingly studied, offering promise for a treatment that saves lives by acting against the disease. The gene responsible for causing CF is located on the long arm of chromosome 7, the most common mutation being DF508. The defective gene responsible for CF causes production of a protein called Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) that may be affected in different ways: it is either missing or non- or poorly functioning. The consequence is the inability of epithelial cells to carry adequate chlorine in all organ system, except the brain, and elevated sweat chloride and sodium concentrations (3). With the discovery of the gene that causes CF, it became a target disease for gene therapy because it is a monogenic disease and the lung is easily accessible (7). The basic concept is to identify the defective gene and correct the defect with a normal gene. The first gene therapy called “germline therapy” helps both the patient

being treated and his/her children. Another gene therapy is “somatic therapy” which consists in replacing the defective gene, but the change will not be passed on to the next generation (8).

Today, the gene therapy remains controversial, there are pros and cons arguments of gene therapy. Supporting arguments for gene therapy claim that the most important factor in the development of gene therapy is represented by the fact that there is only one way to cure the disease by replacing the defective gene with a healthy copy. Due to the fact that gene therapy targets carrier’s reproductive cells, it is likely that any child-carrier goes on to have would be free of the defective gene, and, on a larger scale, the disease to disappear completely. When successful, gene therapy has advantages over drug therapy which only reduces symptoms (9,10). But there are arguments that urges caution, the first limitation being related to how to obtain the normal gene to replace the defective one. After inserting the correct gene into the cell, the next problem is getting it to go to the right place. This is done with the help of some vectors containing the correct gene, either viral (adenovirus attenuated) or non-viral (cationic liposomes), but there is no guarantee that the vector carrying the healthy gene reaches the right place. Results are not sure of the long term effects of gene therapy or if it can be repeated (8,9).

As so far all studies on gene therapy in CF were conducted in adolescents and adults in which the clinical manifestations caused irreversible tissue damage, today we speak about *in utero* gene therapy. This would have the following advantages:

- acts on organs/tissues that will not be later on available, the onset of the destructive process being early;
- can induce tolerance to the vector and transgenic protein;
- can provide prenatal prevention of the disease.

For a good understanding of the ethical issues of gene therapy, two concepts are essential:

1. There is a consensus that gene therapy should be treatment, that is correction in good faith of the disease, rather than enhancement, meaning improvement of the human species.

2. Somatic versus germline gene therapy: germline therapy is “open-ended” and involves invasive experiments on human embryos, the effects of which extend into the future. From an ethical standpoint this kind of therapy would be the equivalent of a clinical trial in subjects who did not consent, and the ethical evaluation of this therapy depends on the ethical principles on the human embryo and

the moral principles of those who approve or not the early experiments (11).

Gene therapy and must comply with the basic ethical principles applicable to other therapies:

- favorable benefit – risk ratio;
- fairness in selecting subjects (principle of justice);
- specific informed consent (principle of respect for persons) (11).

## TRANSPLANTATION IN CF

Since 1985, lung transplantation has become an option for some patients with CF. In end-stage disease, the only effective treatment is lung transplantation. Patients selected for lung transplantation must have severe respiratory failure despite proper therapy, Shwachman score below 40, oxygen saturation below 90%, severe impairment of quality of life, and to want a transplant. However, the estimated long-term survival of the transplant candidate should be long enough as not to influence the success rate (12). The decision about the need for transplantation should be made about two years before surgery, sufficient time to assess the patient and find the donor. An argument in favor of lung transplantation in patients with CF is that it is performed at younger ages, and thus the patients have a longer survival. The deficit in cadaveric lung donations has led to living-donor lobar lung transplantation. Studies have shown that one-year survival of these patients is similar to that of those receiving cadaveric lungs (13). Programs that include living-donor lung transplantation require long-term follow-up and reporting the complications to the donors as a moral obligation. CF patients are not discriminated between those who require single versus bilateral transplantation. Given the significant morbidity and mortality and long-term risks of lobectomy, the voluntary consent of the donor is required. He/she must receive all information necessary for making the decision to donate. The most relevant information is considered that related to the short and long-term deterioration of donor's health (12). Removal of organs from deceased persons is only permitted with the written consent of at least one adult family member or relative. If the deceased had already registered as a donor by an affidavit the consent of family members is not required (14).

## SEXUAL AND REPRODUCTIVE HEALTH IN ADOLESCENTS WITH CF

Improvements in the treatment and management of CF have led to a steady increase in life expect-

tancy of these patients. The life span of CF patients has increased, as has their desire to become parents. Consequently, issues regarding sexual and reproductive health have become relevant for both patients and their families (15). Timing of puberty can lead to psychological problems. Many adolescents with CF have problems related to their physical appearance because puberty is delayed, and to the fact they look different from healthy adolescents may cause stress. The amount and quality of sexual and reproductive health information differs with patient's sex (14).

### a. Fertility in women patients

Women with CF have normal genital tract and although initially thought to be less fertile than healthy women, subsequent studies have shown that they have a fertility rate similar to that of the general population (12). In making the decision to become a mother, women with CF should consider three aspects that raise important ethical issues:

1. Risk of transmitting CF to their offspring: she must make a decision knowingly, aware of the risk of having a child with CF, and to take the risk. Genetic counseling is mandatory before making the decision to have a child. Being an autosomal recessive disease, each child of a woman with CF may be at least a carrier. They increase the carrier rate and over time the number of people affected by the disease. The number of children born to women with CF is approximately 100/year. The large number of mutations associated with CF makes the detection of all carriers impossible. Another possibility is the child to have the disease, this depending on the carrier status of the father: if the father is a carrier, the risk of having the disease is 50% for each child. If one partner is a carrier, the couple has the following options:

- not to become parents;
- use donor eggs or sperm;
- determine the fetal genotype in utero (12,16).

Another ethical issue is raised by partner screening for finding out whether there is a risk of having a child with CF and its selective role in termination of pregnancies with affected fetuses.

2. Maternal and fetal health: some studies report that pregnancy may be normal in patients with CF, but there are studies that have shown the occurrence of maternal complications and even increased mortality. Thus, changes during pregnancy can adversely affect the severe pulmonary disease (may increase respiratory rate, oxygen consumption, and the increase in blood volume and cardiac output can cause heart failure). Therefore, pregnancy in CF patients should be considered high risk and pulmonary and nutritional status should be monitored.

3. Long-term course, with the likelihood of premature death.

#### **b. Fertility in men with CF**

Except for 1-2%, men with CF are sterile, the most common cause being the congenital anomalies of the vas deferens. Frequently, information for adolescents and their parents are incomplete. Insufficient or incorrect information may lead to misinterpretation, confusion of male infertility with impotence [1]. Alternative methods of conception are artificial insemination with donor sperm and microsurgical sperm aspiration and injection into oocytes. Intracytoplasmic sperm injection – technique allowing immature sperm injection into the oocyte – led to improved performance of in vitro fertilization, and to scientific and ethical controversy regarding the use of immature gametocytes. Before becoming a father, a man with CF should be informed about his health status and long-term outlook, such as the risk of premature death. These issues should be discussed with the partner (13). Child adoption by persons with CF is difficult for various reasons. One of these reasons is the fact that for adoption agencies the best interest of the child outweighs the rights of the prospective adoptive parents. The loss of a biological parent causes child distress, and a subsequent loss of the adoptive parent with CF during his third-fourth decade of life determine agencies to exclude them from the waiting list. In this situation, some parents with CF turn to private or foreign adoption agencies, omitting to inform them about their disease. For ethical and legal reasons this practice should be discouraged (12).

Some questions about male fertility remained unanswered:

- what is the appropriate age to discuss male infertility?;
- what is the effect of information on fertility at different ages;
- what value of semen analysis confirms infertility;
- who should talk about sexual and reproductive health (13).

### **TRANSITION FROM CHILD TO ADULTHOOD**

Transition is the passage from one stage of life to another accompanied by physical, mental and social changes temporarily disrupting the normal life and requiring a period of adjustment (13). During infancy and toddler period pediatricians interact with parents in making decisions about the care of the child with CF and adherence to treatment. As

they grow, children with CF wish to take an active role in meeting medical decisions. In adolescence adherence to treatment depends mostly on the patient, and involvement of the CF patient is a prerequisite for increasing compliance (11). The transition of the CF patients from adolescence to adulthood is more difficult because they have to gain medical independence and to face the reality that there is no radical medical treatment (3). Internists should be able to act as educators for these patients and to collaborate with other specialists (gastroenterologist, pulmonologist, surgeon, diabetologist, gynecologist, psychologist). Transition to adult care can be achieved either directly (not recommended) or progressively with a period of overlap of care between pediatric and adult medical teams.

Key persons involved in the transfer are:

- CF patient: for it is important to feel supported in decision making by family and caregivers;
- patient's parents: for them transition is an emotional step. At adolescence, part of the care they provided is transferred to their child, and this may cause anxiety and loss of control over the child;
- pediatric and adult care services: pediatric services should educate parents and teens about the latest advances in adult care. In turn, the staff of adult care services has to meet with the teenager and his family and to establish a partnership and use the experience of the pediatric care centers (15,17).

Multidisciplinary communication between specialties is essential for the young adult who wishes to receive information on treatment.

### **CONCLUSIONS**

1. Optimal care of children and adults with CF requires not only the use of the latest medical advances, but also focusing on the ethical issues that accompany these developments.
2. The benefits of newborn screening for CF outweighing its risks, its introduction is justified.
3. Gene therapy offers the prospect of effective treatment and cure which no other medical treatment does.
4. The decision to perform transplantation in patients with CF involves comparing the survival with and without transplantation, as well as assessing the quality of life.

5. Physicians responsible for the treatment of adults with CF do not have the right to pre-

vent them from becoming parents, but all ethical issues should be discussed.

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