CASE REPORT

Mild Cystic Fibrosis. A Case Report

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ABSTRACT

Context Cystic fibrosis is the most common autosomal recessive genetic disease in Caucasian population. Extending knowledge about the molecular pathology on the one hand allows better delineation of the mutations in the cystic fibrosis transmembrane regulator gene and the other to dramatically increase the predictive power of molecular testing. **Case report** This study wants to underline that the identification of individuals with atypical cystic fibrosis can sometimes present particular difficulties of interpretation. **Conclusion** On that ground, if there is a strong clinical suspicion, it is always advisable the biochemical study by performing the sweat test, followed by sequencing of the cystic fibrosis transmembrane regulator gene.

INTRODUCTION

Cystic fibrosis (CF) is the most common autosomal recessive genetic disease for the Caucasian population. In Italy, the disease occurs in 1/2500 to 1/3000 Caucasian newborns, with a carrier incidence ranging from 1/26 to 1/30 in the general population [1, 2]. CF is a complex multisystem disease related to the buildup of thick, sticky mucus that can damage many of the body's organs (epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. The *CFTR* gene is located on the long (q) arm of chromosome 7 (7q31.2) [3, 4]. More than 1.800 mutations in the CFTR gene have been identified [5]; many of which are so rare as to be called 'private' as they are only present within individual families.

Besides the classical form of severe disease, other clinical forms of CF have been identified and called "atypical" forms. These one show monosymptomatic phenotype (recurrent pancreatitis, congenital bilateral agenesis of the vas deferens, asthma, bronchiectasis) and benign prognosis than the classic form of CF.

Recently, the studies on the genetics of CF have followed different directions, showing that there are a number of proteins that interact with the CFTR increasing up to 6 times the activity, like the SLC26 carrier family. Mutations in these genes may result in a defective activation of CFTR [6].

This paper wants to emphasize that the identification of individuals with atypical cystic fibrosis can sometimes present particular difficulties of interpretation.

For this reason, if there is a concrete clinical suspicion of CF, it is always advisable, to perform the biochemical study by the sweat test, followed by sequencing of the CFTR gene.

MATERIALS AND METHODS

The diagnostic pathways in assisted reproductive technology (ART) centres is aimed at finding the causes of infertility in couples and to implement procedures to solving the problem.

A couple came to our attention to do these exams: kariotyping and CFTR molecular screening such as preliminary exams for assisted reproduction cycle.

Pelvic ultrasonography, performed to the lady, showed the presence of a retroflexed uterus, with a normal profile, echostructure and dimensions. Her endometrium had a normal echographic aspect. Both her right and left ovary were normal with respect to dimension and form, without any liquid effusion.

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A hysterosalpingogram confirmed the normal uterus-tubal anatomy. Serum anti-ovarian and anti-adrenal antibodies were absent. On third day of the menstrual cycle the patient had normal levels of gonadotropins (LH: 6.4 IU/L and FSH: 7.3 IU/L). Her thyroid-stimulating hormone, free tri-iodothyronine and free thyroxin hormone levels were normal, while the levels of anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies were very normal.

The husband had regular pubertal development, absence of cryptorchidism, absence of sexually transmitted diseases or signs of genital inflammation and normal endocrine function.

By history the gentleman reported to suffer from chronic sinusitis and who had previously undergone two operations for nasal polyposis. Specialised diagnostic tests showed that the man did not suffer of bronchitis or bronchopneumonia. The biochemical pancreatic and hepatic parameters were within normal limits (normal values of steatocrito and fecal elastase). Urological examination showed bilateral absence of the vas deferens. Two semen collections also revealed azoospermia.

For these reasons, were performed the following tests:

- Analysis of the karyotype of both spouses. Karyotype was obtained from T lymphocytes extracted from peripheral blood using the common culture technique. The obtained chromosomes were banded with Q-banding methods using quinacrine.
- Sweat test (Gibson and Cokee). Made only to the husband for the presence of azoospermia and bilateral agenesis of the vas deferens.
- Molecular analysis of the *CFTR* gene was performed following these steps:

– DNA isolation, starting from 25µl of blood venous collected in EDTA-K3.

– Polymerase chain reaction (PCR) and reverse hybridization. The test has a sensitivity and a specificity of more than 99%. With a direct analysis of 60 mutations of the *CTFR* gene.

The patients who tested negative or with a single mutation detected by reverse dot blot and with a clinical suspicion of atypical cystic fibrosis were analyzed with a complete scanning of the codificant region, through amplification and direct sequencing of 27 exones of the *CFTR* gene.

RESULTS AND DISCUSSION

Both spouses had a normal karyotype. The sweat test resulted positive (>60 mmol/L) for the husband. From a sweat collection of 198 mg, we found Na^+ concentration of 99 mmol/l and Cl^- concentration of 118 mmol/L. The molecular analysis by reverse hybridization confirmed that the husband appeared, heterozygous for G542X mutation (c.1624G>T; p.Gly542X). Since the man had clinical signs compatible with a framework of atypical cystic fibrosis, it was necessary the sequencing of the complete CFTR gene.

The sequencing of the gene revealed a second mutation, exactly the E831X (c.2491G>T; p.Glu831X). For that reason the man resulted to be compound heterozygote (G542X/E831X) for the CFTR gene.

The lady was not carrier of one of the 60 mutations studied by reverse dot blotting. To prevent that the lady could be a carrier of a mutation not included in the 60 studied, we also proceeded for her to the sequencing of complete CFTR gene that confirmed the absence of mutations.

In this way we have explained to the spouses that the possibility of conceiving a son or daughter affected from CF is zero; and that all the children will be carriers of the mutation G542X or mutation E831X.

The genetic structure found in the husband, shows a very good chance to find sperm in the testicles. Consequently spouses may try to become biological parents, undergoing a cycle of assisted reproduction (IVF).

CONCLUSIONS

This study wants to underline that the identification of individuals with atypical cystic fibrosis can sometimes present particular difficulties of interpretation. On that ground, if there is a strong clinical suspicion, it is always advisable the biochemical study by performing the sweat test, followed by sequencing of the CFTR gene.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying.

Conflicting Interest

The authors had no conflicts of interest

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