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Original Article

Highlighting the impact of cascade carrier testing in cystic fibrosis families☆

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Abstract

Background: Cascade carrier testing within cystic fibrosis (CF) affected families offers relatives of CF patients the opportunity to know their status regarding the mutation that segregates within their family, and thus to make informed reproductive choices. As an Australian study has recently shown that this test seemed underused, we searched to assess uptake of this test in a European area where CF is common, and to report its public health implications.
Methods: This study relied on 40 CF-affected families from western Brittany, France. Investigations included drawing of family trees and registration of carrier tests performed in those families.
Results: Of the 459 relatives eligible for testing, 185 were tested, leading to an adjusted uptake rate of testing of 40.7% (95% CI: [34.1%; 47.3%]). The main predictors for having testing were being female ($p = 0.031$) and having a high prior risk ($p < 0.001$). Planning a pregnancy or expecting a child (reported in at least 38.4% of tested relatives) also appeared critical in choosing to be tested. Overall, carrier testing allowed to reassure more than 1/4 of the relatives and to detect five new 1-in-4 at-risk couples who then requested prenatal diagnosis.
Conclusions: This observational study assesses, for first time in Europe, uptake of CF cascade carrier testing within CF families, which is a critical tool to reassure non-carriers and to detect early new at-risk couples.

Keywords: Cystic fibrosis; *CFTR*; Cascade carrier testing; Genetic counseling; Predictors

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; GEE, generalized estimating equations; NBS, newborn screening; SD, standard deviation.

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1. Introduction

Despite great improvements in disease management that allow more than half the patients to reach adulthood, cystic fibrosis (CF) remains a life-threatening condition [1]. The identification in 1989 of the gene responsible for this autosomal recessive disease (the *Cystic Fibrosis Transmembrane conductance Regulator* (*CFTR*) *gene*) [2–4] made possible genetic diagnosis for CF patients, and thus cascade carrier testing for family members.

Cascade carrier testing offers relatives of CF patients (who have an increased risk of being themselves carriers of the mutation that segregates within their family) the opportunity to know their status regarding the family mutation. The term "cascade" reflects the fact that the test stems from an index case: it is first offered to the relatives of the CF patient and, in a second time, to their spouses if the relatives are found carrier. The ultimate goal of this test is to reassure non-carrier relatives, but also to allow for early detection of couples with a 1-in-4 risk of having a CF child, who will then be able to make informed reproductive choices (such as use of prenatal diagnosis). In the absence of mutation-specific therapy for all patients, cascade carrier testing within families remains therefore a major prevention tool in the context of serious genetic diseases [5–8].

Cascade carrier testing should not be confused with population-based carrier screening that aims to identify all CF carriers in a given population. Such programs are undertaken in some regions around the world, as in Australia, in the Veneto region in Italy or in the US [9–11].

To date, few studies have been published on cascade carrier testing within CF families [12–18], and most of them reported results of active programs (in regard to information or recruitment of relatives). Globally, relatively low rates of testing uptake have been observed in relatives of affected patients. In an observational study conducted in Victoria (Australia) in 2010, McClaren et al. [18] reported an uptake rate of testing of 11.8% in relatives of screened children born during 2000–2004. To our knowledge, no measure of uptake of cascade carrier testing in CF families has been performed in France or in Europe, from an observational study design based on the examination of clinical practices.

The present study aims to assess the uptake of cascade carrier testing in relatives of CF patients born over a 25-year period (1980–2004) in a district of western Brittany (Finistère, France), where CF is particularly common [19]. It determines the proportion of relatives tested, identifies factors influencing the choice of having testing, and reports the public health implications of this test.

2. Population and methods

2.1. Study design and setting

We conducted an observational retrospective study in the district of Finistère, an area of 900,000 inhabitants in western Brittany (France) where the incidence of CF is high (~1/2500 live births) [19,20]. The high mutation detection rate obtained in that population shortly after the discovery of the *CFTR* gene [21] has enabled clinicians to offer early an efficient and efficacious testing process to identify carriers in CF families.

When CF is diagnosed in a child, his parents have the opportunity to meet a genetic counselor, who explains the disease, but also the implications of the diagnosis for future pregnancies and the availability of cascade carrier testing for their relatives. As until recently the transmission of the genetic information within families could exclusively be done by the parents of the CF child, they were invited to inform their relatives about their possibility of having testing. A recent change in French law henceforth allows GPs to directly inform relatives of CF patients on their risk and the possibility of getting tested.

Cascade carrier testing, which is offered during a genetic counseling session, consists first in determining whether the relative does or not carry the *CFTR* mutation that segregates within his/her family. If the relative appears to be non-carrier of this mutation, the study is stopped and he/she can be reassured regarding his/her offspring. Conversely, if the relative is found to be carrier, a *CFTR* gene analysis is proposed to his/her spouse. The guidelines are to use of a commercial kit (of 30 mutations) that enables to detect 85% of the *CFTR* mutations in the French population. If no mutation is identified in the spouse by this strategy, a residual risk of CF is given to the couple. On the other hand, if one mutation is also identified in the partner, the couple has a 1-in-4 risk of having a CF child. Genetic counseling is then offered to the couple who may opt for prenatal diagnosis for current or future pregnancies. Such tests are covered by the French Health Insurance.

2.2. Study population

This study was conducted from families of CF patients born in Finistère over the 1980–2004 period. It was approved by the ethical committee of the University Hospital of Brest.

The identification of patients eligible for the study was facilitated because a registry of CF patients born in Brittany since the 1970s was set up several years ago [19], and because Brittany was a pioneer back in 1989 in setting up a CF newborn screening (NBS) program [22].

The flow chart of the inclusion/exclusion criteria in the study is presented in Fig. 1. Over the study period, 128 CF patients were born in the district of Finistère. Nine of them were *de facto* ineligible for the study: two were adopted and seven already had a CF-affected sibling born during the study period (only one patient per family, the first diagnosed, could be included). In all, 119 patients were eligible for the study, but only 109 could be informed of the study as eight were lost to follow up and two had a difficult family context. At the end of the inclusion period (Dec. 31st, 2014), 40 families agreed to participate in the study.

2.3. Data collection and management

A two-step strategy was used to collect data required for the study:

1) First, patients (or their parents) were asked to fill out a consent form and to provide a family tree (limited to all