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Original Article

Misdiagnosis of cystic fibrosis — Experience from Germany

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Abstract

Background: Misdiagnosis of cystic fibrosis (CF) is rare. We investigated patients with misdiagnoses of CF in Germany, and compared patients diagnosed before and after 1990.
Methods: We analysed data from the German CF quality assurance project and rechecked the data with CF-centre directors.
Results: Between 1989 and 2004, CF diagnoses were withdrawn in 51 patients after 5.79 years (median), whose diagnosis was based on nonspecific symptoms between 1979 and 2001 at the median age of 4.33 years. CF transmembrane conductance regulator (CFTR) dysfunction was indicated by unreliable sweat tests (45.1%), pathologic sweat chloride (37.3%), genetic tests (3.9%), and nasal potential difference measurements (13.1%). Patients diagnosed after 1990 were older (6.13 vs 1.21 years), more frequently fulfilled the diagnostic criteria (77.4% vs 20%) and experienced respiratory symptoms (83.9% vs 50%).
Conclusions: To detect misdiagnoses of CF, CF-centres should re-evaluate patients with atypical courses and new or transferred patients.

Keywords: Cystic fibrosis; Diagnostic errors; Misdiagnosis; Sweat; Cystic fibrosis transmembrane conductance regulator

1. Introduction

Cystic fibrosis (CF) is diagnosed based on at least one typical clinical feature, a positive newborn screening result, or a history of CF in a sibling, and confirmation of cystic fibrosis transmembrane regulator (CFTR) protein dysfunction [1–3]. The clinical features of CF can be highly variable, including specific symptoms like pancreatic insufficiency and nonspecific ones like chronic cough and malnutrition [2]. Until the discovery of the CFTR-gene in 1989 [4], CFTR dysfunction could only be detected by a sweat test. High false-positive [5] and false-negative [6] rates were reported during this time, attributed to inaccurate methodology, technical errors, and patient physiology. Several single centre reports from the UK [7–9] and the US [10,11] described 54 patients who had been misdiagnosed based on clinical features, despite a normal or false-positive sweat test, between 1970 and 1994. Since 1990, the diagnostic possibilities have been expanded by CFTR genotyping and nasal potential difference measurement (NPD) [1], and sweat testing has undergone standardization and quality controls [12,13]. To determine the extent of the problem of misdiagnosis, we investigated the individual diagnostic approach, course, and final diagnosis of patients with a misdiagnosis of CF based on data from the German CF registry and data from the CF centre, and compared the age and symptoms at diagnosis and the diagnostic approach to patients diagnosed before and after 1990.

2. Patients and methods

The German CF quality assurance (CFQA) project includes a patient registry, which contains relevant diagnostic, clinical, and laboratory data, respiratory function test results, and categorised CF treatments and complications. The patient registry was founded in 1995. Inclusion criteria are a clinical diagnoses of CF by a

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clinician, independent of formal criteria. Basic sheets contain demographic data, date of the CF diagnosis, sweat test results, genotype, and initial symptoms (categories: gastrointestinal, respiratory, meconium ileus, rectal prolapse, siblings with CF, and positive screening test).

It is possible to report withdrawal of the diagnosis (date, reason). The yearly follow-up sheets (data from a visit near birthdays) deal with nutritional status, respiratory function, categorised CF treatments, and complications.

Up to December 31, 2002 (data set 01.06.2003), a CF diagnosis was withdrawn in 47 patients. We analysed the registry data (basis sheet; nutritional status, lung function, and medication at the last yearly follow up visit), asked the CF-centre directors, who diagnosed the patient and/or withdrew the diagnosis, to confirm or correct the registry data, answer additional questions (e.g. kind of genotyping, diagnosis of exocrine pancreatic function, final diagnostic approach, and final diagnosis), and to report additional patients with false-positive diagnoses who were not included in the registry. Using this strategy, we confirmed the withdrawal of the diagnosis in 42 of 47 patients, and 9 additional patients were also reported. The 5 patients whose withdrawal was not confirmed were mistakenly registered as CF patients, and had never been diagnosed as CF-patients. The data of the remaining 51 patients were analysed. In 6 cases (11.8%), we only have unconfirmed registry data and our questionnaire was not answered. Missing values were not analysed.

2.1. Statistical analysis

Statistical analysis was performed using the Mann–Whitney test (for median age at diagnosis) and Chi-square test (fulfilling vs not fulfilling diagnostic criteria). Fisher's exact test (symptoms at diagnosis) was used to compare patients diagnosed before (≤) and after 1990. A p-value < 0.05 was considered statistically significant. All calculations were made using SPSS (release 19.0.0; IBM, Armonk, USA).

3. Results

We report 51 patients with a misdiagnosis of CF. CF was initially diagnosed at a median age of 4.33 (min 0.07, max 52.94, mean 6.12 ± 8.02) years between 1979 and 2001. Patients diagnosed before 1990 (n = 20; median age 1.21 years) were significantly younger than patients diagnosed after 1990 (n = 29; median age 6.13 years) (p = 0.006) (Fig. 1). During the first year of life, 17.6% were diagnosed, and one patient was diagnosed as an adult (2.0%). The male:female ratio was 1:1.22. The ethnic background was mostly Caucasian (88.2%), Turkish (5.9%), others (3.9%), or remained unclear (2.0%).

Clinical symptoms leading to the diagnosis of CF were isolated pulmonary symptoms (37.3%, mainly chronic cough and airflow obstruction), isolated gastrointestinal problems (23.6%, mainly malnutrition), combined pulmonary and gastrointestinal problems (33.3%), and unclear symptoms in a single case. History of CF in a sibling or a positive screening test were the only phenotypic features of CF, occurring in one patient each. A positive family history was reported in 7 patients (13.7%). In contrast to gastrointestinal symptoms, respiratory symptoms occurred significantly more often in patients diagnosed after 1990 (83.9% vs 50.0%; p = 0.013) (Fig. 2).

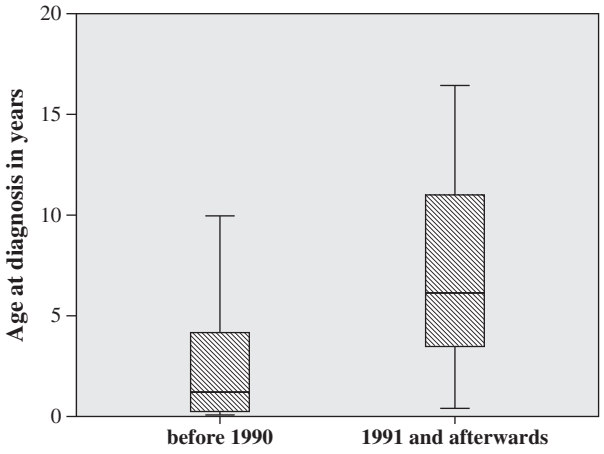

Fig. 1. Age at diagnosis. The median (line within the box), 25% and 75% percentiles (box top and bottom), and range (lines and whiskers) are indicated for each age group. One outlier diagnosed after 1990 (aged 52.9 years at diagnosis) is not shown.

CFTR dysfunction was detected by abnormal sweat sodium or conductivity in 45.1% of all patients. In 37.3%, at least one sweat chloride measurement was >60 mmol/l. In 7 patients (13.7%), CFTR dysfunction was diagnosed only by NPD. This was done at one centre in Germany based on a pathologic basal PD as the only diagnostic criterion [14]. Genetic testing was done in 66.7% and identified one F508 homozygote (sweat chloride, 17 mmol/l) and one positive indirect gene analysis (sister of a CF patient who refused sweat testing). Of all patients, 54.9% fulfilled the diagnostic criteria for CF according to the guidelines [1]. Patients diagnosed after 1990 fulfilled the diagnostic criteria more often than patients diagnosed prior to 1990 (77.4% vs 20%; p = 0.000) (Fig. 3).

The initiative to revaluate the patients was instigated by CF centres (93.3%) and a minority (8.9%) of patients or parents. The main reason for revaluating the diagnosis was an atypical clinical course (91.1%), diagnostic studies (6.7%), and non acceptance of the diagnosis by the parents (2.2%).

The patients were revaluated between 1989 and 2004. The diagnostic approach was sweat chloride (37.7%), genotyping (91.8%, including sequencing in at least 37.3%), and electrophysiology (NPD or intestinal current measurement [53.3%]) [2,15]. Sweat tests were generally normal, genotyping failed to discover two CF-causing mutations, and NPD/ICM did not confirm CFTR dysfunction. In 20.0%, all three diagnostic tests were used (Table 1). Transiently-elevated sweat chloride levels led to a misdiagnosis in 19 of our patients.

Median age at withdrawal was 12.65 (min 1.96, max 57.63; mean ± SD, 13.96 ± 8.71) years. Nearly a quarter of patients were adults at this time (23.5%). The patients were treated as CF-patients for a median of 5.79 (min 0.41, max 24.96; mean ± SD, 7.83 ± 6.30) years. The diagnosis was withdrawn within 12 months in 11.8%, and after 10 years in 29.4% of all patients. At the time of revaluation, 20.8% were malnourished and 19.0% had a forced