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ORIGINAL ARTICLE

Cystic fibrosis – characterization of the adult population in Portugal

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Abstract
Introduction: The incidence of cystic fibrosis (CF) in Portugal is estimated at 1:8000 live births, although there is a lack of accurate statistics. The average life expectancy has been steadily increasing and CF is no longer an exclusively pediatric disease.
Objectives: Characterize the Portuguese adult population with the diagnosis of CF.
Methods: Retrospective study based on clinical data of adult CF follow-up patients in the three specialized centers in Portugal where all of CF patients are seen, during 2012.
Results: In 2012, there were 89 follow-up patients, 48 (54%) female and 15 (17%) lung transplanted. The average age was 31.3 ± 9 years. The median age at diagnosis was 13 years and 34 (38%) were diagnosed in adulthood. The most frequent mutation was F508del (54.9%). Of the 89 patients, 49 patients (56%) had pancreatic insufficiency, 7 (9%) were diabetic and 42 patients (47.7%) had a body mass index (BMI) <20 kg/m^2. As to ventilatory function, the average value of the forced expiratory volume in 1 s (FEV_1) was 58.45 ± 28.59%. Only one of 77 patients did not have chronic airway infection. The most commonly isolated germ was methicillin-sensitive *Staphylococcus aureus* in 49 patients (55%). During 2012, two patients (2.2%) died at the ages of 21 and 36 years.
Discussion: This study is the first description of the Portuguese adult CF population, which is particularly important since it can give us a better understanding of the real situation. A significant percentage of these patients were diagnosed in adulthood, which highlights the need for diagnostic suspicion in a patient with chronic lung disease and atypical manifestations.

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Introduction

Cystic fibrosis (CF) is the most common autosomal recessive monogenic disease in the Caucasian population. Its incidence in Portugal is estimated at 1:8000 live births, based on preliminary results obtained from the neonatal screening pilot project, ongoing for two years. This pilot project encountered almost only F508del homozygous, therefore its true incidence is perhaps underestimated. However, precise statistical data does not exist. In all 28 European Union countries, the prevalence is estimated to be 0.74 per 10,000 individuals.[1] The average life expectancy has been steadily increasing and CF is no longer an exclusively pediatric disease, affecting more adults than before. In the 1940s to 1960s CF was usually fatal in early childhood because of the consequences of recurrent pulmonary infection and malnutrition due to pancreatic failure and subsequent maldigestion of nutrients. Initial improvements in care included the introduction of pancreatic enzyme replacement therapy in the 1960s and enteric coated enzymes in the early 1980s to treat pancreatic insufficiency in combination with a high calorie and high fat diet. Systemic antibiotic therapy for lung infection and the development and use of inhaled antibiotic therapies over successive decades have been important therapeutic developments. The introduction of mucolytics including dornase alpha, hypertonic saline and more effective methods of airway clearance have contributed to the major therapeutic advances from the 1970s to the current era. These and other supportive therapies for complications of CF have been delivered by multidisciplinary teams in CF centers. Centralized care with dedicated CF teams has become and remains the cornerstone of care delivery in CF.[15] According to the European Cystic Fibrosis Society patient registry (ECFSPR) data, the median predicted age of survival at 2010 was 43.5 years in UK.[2] In Portugal there is no national data, however, according to CF adult follow-up patients in specialized centers, the average age is 30.7 years.[3] In our country there are 300 follow-up patients in specialized CF outpatient clinics (less than expected considering the incidence in Portugal), and approximately one-third are adults. In this group, pulmonary disease tends to be more advanced and associated with several co-morbidities such as diabetes, metabolic bone disease, cancer, toxic effects and complications associated with lung transplantation.[4]

CF is caused by mutations in the long arm of chromosome 7, encoding the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which is expressed predominantly in the epithelial cells.[5] So far more than 2000 mutations have been identified,[6] the most common is F508del and the others are rare.[7] Mutations in this gene cause changes in the transepithelial ion transport of chloride and the organ most affected is the lung, which is the greatest contributor to the morbimortality. It results in impaired mucociliary clearance and predisposition to airway infection.[5] Surprisingly, infections are caused by a limited number of bacteria. In adults, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most frequent microorganisms.[8] Recent reports document an increasing incidence of new Gram-negative pathogens such as *Stenotrophomonas maltophilia, Alcaligenes xylosoxidans* and *Burkholderia cepacia complex*.[9]

Even when aggressive treatment of the respiratory disease is employed, there is a progressive decline in lung function, with a moderate-severe impairment present in 60% of adults.[10] When lung function is severely compromised lung transplantation may be indicated. In these patients, bilateral lung transplantation is the only option, given the chronic bronchial infection.

The disease is multisystemic and affects all organs that express CFTR, including not only lung but also pancreas, intestine, biliary tract, vas deferens, sweat and salivary glands.[11]

Exocrine pancreatic insufficiency is present in 85% of patients with CF and the clinical manifestations (such as steatorrhoea and poor nutrition) are mostly dealt with by diet and pancreatic enzyme replacement. In some patients (8–15%), as time progresses, there is destruction of insulin-producing cells, resulting in endocrine pancreatic insufficiency, manifested by diabetes mellitus. Pancreatic sufficiency (15%) may be present at an older age and usually patients have milder lung disease and normal or borderline sweat electrolyte values.[11]

Usually only a small percentage of patients (3–5%) have liver disease, which manifests clinically as neonatal jaundice, hepatic steatosis or biliary cirrhosis. It is also possible to observe a micro-gallbladder and increased incidence of gallstones (12% of patients), which normally does not cause any symptoms and does not require treatment.[11]

Recurrent constipation and distal intestinal obstruction syndrome (previously known as meconium ileus equivalent) are features in older patients with CF.[11]

Approximately 97% of males with CF are infertile due to azoospermia attributed to congenital bilateral absence of the vas deferens. Infertility may be the initial presentation for some males with mild disease. However, a male gender CF patient may have children, by puncturing the seminal vesicles, doing sperm collection and *in vitro* fertilization. In the female gender the ovulation is normal, but given the adverse conditions, there is a decrease in fertility due to anovulatory cycles. The presence of thick cervical mucus, which functions as a barrier to sperm, is another factor contributing to lower fertility.[11]

Sweat glands in CF patients do not show any histological abnormalities but have pronounced abnormalities in sodium-chloride homeostasis due to defective CFTR function. The consequence of this defect is a resultant sweat with a relatively elevated concentration of chloride and sodium compared with normal sweat. This landmark discovery led to the development of the sweat test for diagnosis in 1959.[11] An increased concentration of electrolytes in the sweat may result in hyponatremic/hypochloremic dehydration secondary to salt depletion or hypokalemic metabolic alkalosis secondary to chronic salt loss. Once the diagnosis is known and regular salt replacement offered this problem is rarely seen.[11]

Despite the technological advances in recent years, in terms of diagnostic and therapeutic approach, CF remains a progressive and lethal chronic disease.

This study aims to characterize the Portuguese adult population diagnosed with CF followed in specialized centers during 2012.