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ORIGINAL ARTICLE

# Cystic fibrosis – Comparison between patients in paediatric and adult age

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**Abstract** Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians. Although most cases are diagnosed in childhood, diagnosis in adults is apparently increasing.
*Objective:* Evaluate the adult population with CF, comparing patients who were diagnosed before and after 18 years of age.
*Methods:* Retrospective analysis of patients followed in three main medical centres in Portugal in 2012. Comparison of two groups: G1 – patients diagnosed at <18 years and G2 – patients diagnosed at ≥18 years.
*Results:* 89 adults were identified: 61.8% in G1, 38.2% in G2. Gender distribution was similar in both groups. Average age in G2 was higher (38.3 ± 8.4 vs. 26.8 ± 6.1 years, $p < 0.001$). Respiratory symptoms most frequently led to CF diagnosis in all patients, mainly in adulthood. There was a greater percentage of patients homozygous for the mutation delF508 in G1 (43.6 vs. 8.8%, $p = 0.02$). Respiratory and pancreatic function, and body mass index (BMI) showed a higher severity in G1 (G1 vs. G2: FEV1: 54.6 ± 27.3 vs. 29.9 ± 64.6%, $p = 0.177$; pancreatic insufficiency 72.7 vs. 26.5%, $p < 0.001$; BMI 20.2 ± 3.4 vs. 22.2 ± 4.8, $p = 0.018$). *Pseudomonas aeruginosa* and *methicillin-sensitive Staphylococcus aureus* were the most frequently isolated microorganisms. Lung transplantation rate was higher in G2 (20.6 vs. 10.9%, $p = 0.231$) while mortality rate was higher in G1 (0 vs. 3.6%, $p = 0.261$). Hospital admission rate was higher in G1 as well as mortality rate.
*Conclusion:* The results suggest that patients with CF diagnosed in childhood have characteristics that distinguish them from those diagnosed in adulthood, and these differences may have implications for diagnosis, prognosis and life expectancy.


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## Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disease affecting 1 in 2500 newborns among Caucasians.[1]

Its incidence is well documented in Europe where 1 in 2000–3000 newborns are affected.[2] In Portugal, the incidence is apparently lower it is estimated at 1:6000 live births.[3] Currently, however, there are only about 300 CF patients (approximately one-third of whom are adults) in follow-up in specialized centres, fewer than expected considering the incidence value above.

The gene responsible for CF encodes a protein of 1400 amino acids, which functions as a chloride-transport-channel located in the apical epithelial cells, thereby regulating the movement of solute and $H_2O$.[4–6] It was identified in 1989[7–9] and since then, more than 2000 disease-associated mutations have been described.[10]

The most common mutation, which is termed delF508 as a phenylalanine-residue at position 508 is absent, is present in approximately 70% of defective cystic-fibrosis-transmembrane-conductance-regulator (CFTR) alleles.[10]

CF is a highly variable disease and patients are diagnosed with different presentations. Symptoms appear in the first year of life in the great majority of cases but may appear later, even in adulthood with considerable variation in severity and rate of progression.[4]

The gold-standard laboratory method for diagnosing CF is the sweat test but there are other methods such as genetic analysis or the determination of nasal transepithelial potential difference.[11,12] Since 2013 a pilot screening programme for CF, applied to all newborns, has been running in Portugal.

Patients are diagnosed when at least one of these tests positive, identification is associated with one or more phenotypic characteristics, a positive neonatal screening or family history.[12]

Although CF is usually discovered early in life, in recent decades it is no longer an exclusively paediatric disease. The number of adults with CF continues to increase, while the number of children has remained relatively stable over the past decade. In 2013, adults comprised 49.7% of the CF population, compared with 29.2% in 1986.[13] This increase may be due to increased survival, secondary to effective treatment, more diagnostic capabilities with the inclusion of milder forms of the disease, greater availability and improved genetic testing, using more specific and sensitive diagnostic criteria, as well as increased sensitivity to the possibility of medical diagnosis.[14,15]

The first adult CF diagnosis was made in 1946.[16] Since that time, a number of case studies of adults receiving a diagnosis have been reported, and the incidence of delayed diagnosis is expected to increase.

There are a number of reasons for diagnosis as adults. Firstly, mild expression of the disease, absent symptoms or unusual presentations may delay a patient seeking medical attention.[17–19] Secondly, the common perception of CF as a disease exclusive to childhood leads to it not being recognized in adults, especially when the presenting symptoms are atypical.[20,21]

We have found that patients presenting in adulthood appear to be different to patients presenting in childhood. Research has established that, as a group, those diagnosed as adults have variable and atypical presentations, and often have milder disease,[22,23] better, long-term prognosis,[23,24] better lung function, higher rates of pancreatic sufficiency, fewer complications, and longer life expectancy than adults diagnosed in childhood.[24–26]

There is a growing need to identify differences between the groups but there are no published data in Portugal.

The objectives of this study were: (1) to characterize the adult CF Portuguese population, comparing patients who were diagnosed before and after 18 years of age; (2) to determine differences between the two groups regarding demographic characteristics and variables related to CF; and (3) to investigate potential diagnostic and therapeutic implications of these differences.

## Methods

A retrospective analysis of clinical records of patients followed in the three main specialized adult centres in Portugal (Porto, Coimbra and Lisbon) between January 01 and December 31, 2012.

All patients were diagnosed with CF according to the diagnostic criteria in their consensus statement.

These patients were assigned to one of two groups: those diagnosed at <18 years old (Group1 – G1) and those diagnosed at ≥18 years old (Group2 – G2).

Several variables were evaluated (demographic, diagnostic, genetic, mortality, health status, and other related variables) after which the two groups were compared.

The patients were analysed into CFTR mutation classes, and according to these, were subdivided into severe (classes I, II or III) or mild (patients with at least one allele from class IV to VI).

Statistical analysis was performed using SPSS Statistics 19.0.

## Results

Eighty-nine patients with CF were identified, 55 (61.8%) diagnosed at age <18 years of age (G1) and 34 (38.2%) at age ≥18 years of age (G2).

Forty-one patients (46%) were male and 48 (54%) were female. Gender distribution was similar in both groups (G1 vs. G2: women 54.5% vs. 52.9%, men 45.5% vs. 47.1%).

The average age was $31.3 \pm 9.0$ years. There were statistically significant differences in relation to current age, and the average age of patients in G2 was older ($38.3 \pm 8.4$ vs. $26.8 \pm 6.1$ years, $p < 0.001$).

All of the included patients were Caucasian.

The median age at diagnosis was 13, and 34 (38.2%) were diagnosed in adulthood.

Over one-half of adults were women, yet men were more likely to receive a late diagnosis (Table 1).

There were significant associations between age at diagnosis and the condition suggesting the diagnosis (respiratory and digestive symptoms), as noted in Table 2.

Although respiratory symptoms (recurrent/acute respiratory infections, cough, haemoptysis) were the most frequent clinical manifestations leading to the diagnosis in all patients, this is particularly evident when patients are diagnosed as adults (G2 vs. G1: 75.9% vs. 42.6%; $p = 0.005$). Patients in G1 showed a greater variability in conditions

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