An analysis of outcomes in children with cystic fibrosis in a tertiary African centre: A retrospective study

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Background. Cystic fibrosis (CF) is a common genetic disorder in the white population that has become increasingly prevalent in populations of black African descent. Black African children with CF commonly present with nutritional and growth abnormalities.
Objectives. To describe the characteristics of children followed up at the CF clinic at Inkosi Albert Luthuli Central Hospital, South Africa (SA).
Methods. A retrospective chart review of clinical, laboratory and spirometric data of patients registered from January 2013 to January 2016.
Results. Fifteen patients' data were reviewed. Their mean age was 132 months (range 26 - 219) and 53% were male. Sixty percent of these children were white and 26.6% were black African. Collectively, the mean age at diagnosis was 45 months (range 0 - 156), although this was higher in non-whites: 104 months (range 48 - 156) v. whites 1.3 months (range 0 - 3). The white group had better nutritional status with body mass index (BMI) of 17.2 kg/m^2 compared with 14.5 kg/m^2 for non-whites. Age at diagnosis had a negative correlation with weight-for-age *z*-score (–0.61, $p<0.05$) and body mass index (BMI) (–0.54, $p<0.05$). The mean predicted forced expiratory volume in 1 second (FEV_1%p) was 70.0 (range 16.1 - 120.2). FEV_1%p had a positive correlation with weight *z*-score (0.83, $p<0.001$) and BMI (0.59, $p<0.05$). Five of the non-white patients had no mutations identified on the 30-mutation panel test.
Conclusion. CF is diagnosed late in non-white children in SA, affecting their growth and lung function. A genetic panel that includes mutations specific to children of African descent is required.

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Cystic fibrosis (CF) is an autosomal recessive disorder common in white people, which has an increasing prevalence among people of African descent. In South Africa (SA), CF affects 1:2 000 white, 1:4 624 mixed-race and 1:12 000 black people.[1] It is caused by mutations in the CF transmembrane conductance regulator gene located on chromosome 7q31.[2] This results in impaired chloride transport across cell membranes causing characteristic respiratory and gastrointestinal symptoms. The typical clinical presentation is that of recurrent chest infection due to poor airway clearance of mucus, and failure to thrive because of pancreatic insufficiency. This phenotypic presentation has been shown to be different in the context of the SA population, of whom the majority are black African or of mixed-race descent. These populations commonly present with failure to thrive and protein energy malnutrition.[3]

Early diagnosis of CF prevents severe malnutrition and improves long-term growth.[4] In CF, nutrition and growth are determinants of lung health and, ultimately, survival.[5] As a result of improved treatment in recent years, pulmonary function is reported to be better in children who are diagnosed with CF earlier in life.[6] Data from various SA CF centres have shown improvements in lung function[7] and nutritional status[8,9] when compared with previous years, thought to be largely owing to earlier diagnosis, and improved treatment and diagnostic strategies.

Concerning the genetic diagnosis of CF, the most common mutation is *phelF508.del*, which accounts for 81% of mutations in whites.[10] It is less common in mixed-race populations, where it accounts for 53% of mutations, and is rarely found in black South Africans. The most common mutation in black South Africans is *3120+1G>A*, with a carrier rate of 1:90.[1] At least 1 000 babies are expected to be born with CF in SA each year, but with a detection rate of only 46%, most are missed by conventional genetic mutation testing panels.[3] This not only reduces confirmation of CF in black patients but the use of genetic-based prognostic measures and treatment opportunities.

In the clinical course of CF, *Pseudomonas aeruginosa* colonisation has been reported to affect growth and lung function, with those colonised at a higher risk of deteriorating lung health.[11] *P. aeruginosa* status, mean predicted forced expiratory volume in 1 second (FEV_1%p), age and sex have all been shown to predict mortality in children with CF.[11,12]

CF is not a condition confined to a single population. Understanding the differences and similarities in diagnosis, presentation and clinical course is a necessity in the southern African context. We therefore undertook a study to describe the clinical, laboratory and spirometric characteristics of a representative clinic population in KwaZulu-Natal (KZN) Province, SA.

Methods

Study population

A retrospective chart review of all patients attending the CF clinic at Inkosi Albert Luthuli Central Hospital, Durban between the period January 2013 and January 2016 was conducted. All patients attending the clinic during this period were included in the study.

Clinical investigations

Clinical data collected included age at diagnosis, current age, gender, weight, height, body mass index (BMI), race and *z*-scores for weight, height and BMI (calculations according to World

Health Organization guidelines).[13] Weight and height data were collected on the same day as lung function tests were performed. Age was calculated to the time at which data were collected in January 2016.

Laboratory investigations

Data collected included sweat test (Gibson and Cooke, with measurement of sweat chloride), genotype test (30-mutation panel test; Elucigene, UK) and sputum microbiology including colonisation status of the respiratory tract. Chronic colonisation was defined as the persistence of a pathogen on two or more sputum samples over a period of 6 months, as per Leeds criteria.[14]

Spirometry

Pulmonary function tests were conducted for all patients over the age of 6 years; this study reported on FEV_1%p. The highest FEV_1%p value for the most recent year that the patient was seen during the study period was reported for each patient. Date of birth, gender and height, at the time of lung function test, were recorded for calculation of prediction values. Recorded spirometry test results were prebronchodilator values.

Data analysis

Data were recorded and stored using Excel, Microsoft Office Professional Plus 2013 (USA). Data were analysed using Stata 13.0 (StataCorp, USA). Means were calculated for age, weight, height, BMI and FEV_1%p. Pearson correlation was used for comparing non-categorical variables, with $p<0.05$ considered significant.

Ethical clearance

Ethical approval to access patient records was obtained from the Biomedical Research Ethics Committee of the University of KZN (Ref. BCA469/15).

Results

Data were reviewed for a total of 15 patients, with mean age 132 months (range 26 - 219), 53% of whom were male. Forty percent of the children were non-white: 26.6% of black African descent, 6.7% Indian and 6.7% mixed race. Collectively, the mean age of diagnosis was 45 months (range 0 - 156) (Table 1).

On mutational analysis, five of the non-white patients had no mutations identified on the 30-mutation panel used for testing. *phelF508.del* was the most commonly identified mutation in the clinic. Of the white population, four were heterozygote, four homozygote and one unknown. One non-white patient was heterozygote and of mixed-race descent (Table 1).

Age at diagnosis (Fig. 1) was higher in non-whites, at a mean age of 104 months (8.6 years) (range 48 - 156 months) compared with whites at a mean age of 1.3 (range 0 - 3) months. Age at diagnosis had a negative correlation with weight-for-age *z*-score (–0.61, $p<0.05$) and BMI (–0.54, $p<0.05$). The non-white group had poorer nutritional status than the white group, with mean BMI 14.5 kg/m² v. 17.2 kg/m², respectively. The mean FEV_1%p for the study population was 70.0 (range 16.1 - 120.2) (Table 2). FEV_1%p was positively correlated with weight *z*-score (0.83, $p<0.001$) and BMI (0.59, $p<0.05$).

Table 1. Demographics of children with CF

Variable	*n* (%)
Gender (male/female)	8/7 (53/47)
Mean age at diagnosis (months)	45
Ethnic group	
White	9 (60.0)
Black African	4 (26.6)
Indian	1 (6.7)
Mixed race	1 (6.7)
Mutations	
Heterozygous *phelF508.del*	5 (33.3)
Homozygous *phelF508.del*	4 (26.7)
Negative	5 (33.3)
Unknown	1 (6.7)

Only three patients from the study population were chronically colonised with bacterial pathogens. One of these, with chronic *Haemophilus influenzae* colonisation, had a low FEV_1%p of 49.9, BMI 16.6 kg/m² and intermittent *Staphylococcus aureus* growth on sputum. Chronic *P. aeruginosa* infection occurred only in two patients, both of whom were >16 years old. One of these patients was an 18-year-old male with a last recorded FEV_1%p of 31.0 and BMI 15.6 kg/m². His FEV_1%p fell by 18% during the 7-month lung function recording period before his death. The other patient was 16 years old, malnourished (BMI 14.7 kg/m²) with FEV_1%p of 27.9%, and previously colonised with *S. aureus* and *Candida albicans*.

Discussion

CF is a life-limiting condition that has encouraged a considerable amount of research, the bulk of which is undertaken in Western and developed countries, with developing countries such as SA following suit. The diverse populations within SA have presented a broader spectrum for the manifestation of CF.

Table 2. Comparison of age at diagnosis, lung function and growth between white and non-white children

Variable	White	Non-white
Age at diagnosis (months), mean	1.3	104.0
Weight-for-age *z*-score	–1.8	–3.5
FEV_1%p, mean	77.9	56.1
BMI (kg/m²), mean	17.2	14.5
Weight *z*-score	1.7	–3.6

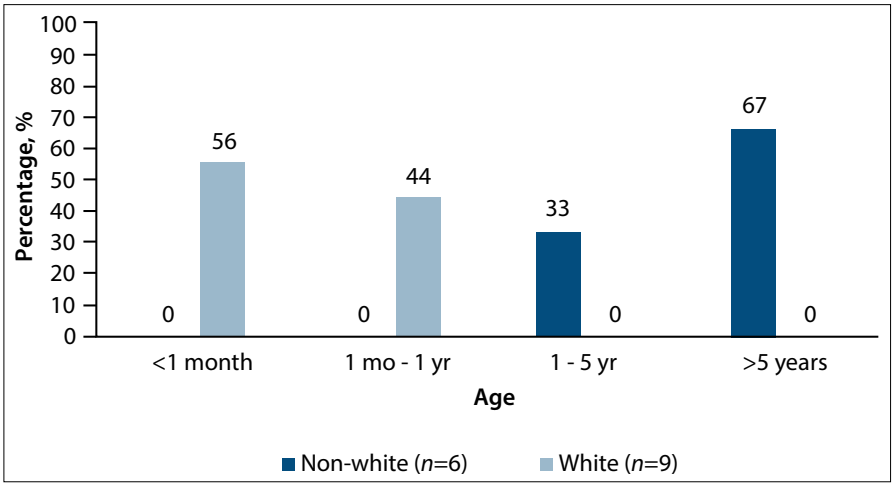

Fig. 1. Comparison of age at diagnosis in non-white v. white children.

Validating other studies, we show that there is a correlation between lung function, growth and age at CF diagnosis.[4-6] We have also shown that for almost half of the population of our clinic, all of whom are black, recognition of CF is difficult, leading to late diagnosis and detrimental effects on disease progression.[15] There may be many reasons for this, including a high prevalence of poverty-associated conditions with similar presentation, i.e. protein energy malnutrition, HIV infection and tuberculosis, which affect the black population in SA to a considerable extent.[3] Another reason may be a high threshold for suspicion, as CF is not common in this population. One study in a Western country showed that features associated with late diagnosis were pancreatic insufficiency and certain genotypes.[16]

In addition, the definitive diagnosis of CF is difficult in this same population, with the current commercial 30-mutation panel proving too narrow for diagnosis.[17] There is a great need for research in this field, as research into the treatment and prognosis of CF currently focuses on individual mutations in patients.[18,19]

Despite our small patient cohort, we were able to observe a trend in morbidity and mortality associated with increasing age and *P. aeruginosa* colonisation.[11] The only patient who died in this study was severely undernourished, had *P. aeruginosa* colonisation and a yearly FEV_1%p decline of 18% – all clinical predictors of mortality.[11,20,21]

Some aspects of CF are similar across populations.[22] However, knowledge about CF in the black population is limited. Despite the small numbers, this study highlights how this field requires dedicated research, with SA in an optimal position for this.

Conclusion

CF is diagnosed late in children of non-white origin in SA, and this negatively affects both their nutritional and pulmonary function outcomes. The current genetic panel misses a large number of mutations in the non-white population and, thus, research in this area is required.

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