

## Letter to the Editor

# Simultaneous Occurrence of Cystic Fibrosis and Sickle Cell Disease in One Patient: Is it a Rare Phenomenon? A Letter to the Editor

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Dear Sir,

Sickle cell disease is an autosomal recessive disorder due to a point mutation in amino acid position 6 of beta-globin (E6V), which results in a change from glutamic acid to valine. It occurs most commonly in blacks, but is also present in non-black populations in the Mediterranean region, the Indian subcontinent, the Caribbean region, and Central America. It is one of the most common genetic diseases in African Americans, with an estimated incidence of 1 in 625 live births, corresponding to a gene frequency of 8%<sup>[1]</sup>.

Cystic fibrosis (CF), also an autosomal recessive disease, is the most common hereditary disease in Caucasian populations, with an incidence in the US of 1 in 4,100 live births and an estimated gene frequency of 3%. CF is less common in the American black and Hispanic populations with a recorded occurrence of 1:14,000 and 1:11,000 live births, respectively, and estimated gene frequencies of 1.7% and 1.9%<sup>[1]</sup>.

CF has been reported before in Saudi Arabia<sup>[2-5]</sup>. The incidence of CF has been estimated to be 1: 4243 live birth<sup>[5]</sup>. The incidence of Hb S for all Saudi Arabian neonates that were screened in one study<sup>[6]</sup> was 14.4% and ranged from 0.8% in Najran to 26.4% in AL-Qurayyat. HbS disease was present in 1.37% and sickle cell trait in 13.1% of all infants<sup>[6]</sup>. In this report, we describe the first case of simultaneous occurrence of both diseases CF and SS disease in the same patient and discuss the course of the disease and review the literature in this subject.

A two and half year old patient presented with a history of recurrent chest infections, vomiting, diarrhea, profuse sweating since 2 months of age and occasional passage of blood with urine with dysuria. He was diagnosed with sickle cell disease (SS disease) at 2 months of age and required repeated blood transfusions due to veno-occlusive crisis. He was found to have hypochloremic, hypokalemic metabolic alkalosis. He was treated with intravenous (I.V.) hydration and antibiotics and was sent to our tertiary care centre for further evaluation.

The patient was a product of Caesarean section, secondary to breach presentation. His family history was significant in that both parents are first cousins. An uncle and an aunt have SS disease and required repeated blood transfusions. One niece died at 2 years of age with cystic fibrosis (CF) in a local hospital and another niece was diagnosed at 6 month of age with CF and SS disease but refused to come for evaluation to our centre.

Initial blood count (CBC) showed WBC  $8.7 \times 10^9$  (normal  $4-11 \times 10^9$ /L). Hemoglobin (Hb) 98 g/L (N 132-172 g/L), Hematocrit (Hct) 0.27 (N 0.38-0.5 Ratio), MCV 77 (N 80-94 fl), Platelet  $306 \times 10^9$ /L (N  $140-350 \times 10^9$ /L), Retic % 4.3 (N < 2%), and Retic count  $159 \times 10^9$ /L (N  $25-85 \times 10^9$ /L), a picture of hypochromic microcytic anaemia with high reticulocytes count. Hemoglobin electrophoresis: showed positive (+ve) for sickle cell disease. Hb A1 level 3.3 (N 96-98%), HbF 22.9 (N 0.0-1.0%), Hb A2 0.0 (N 2.2-3.7%), and Hb S 64.8 (N 0.0-0.0).

A picture of sickle cell disease was evident. Electrolyte and liver profiles were normal. Calcium level (Ca) 2.5 (N 2.1-2.6 mmol/l), phosphate (PO4) 1.97 (N 1.2-1.97 mmol/L), urate was elevated 369 (N 60-240 mmol/L), magnesium (Mg) 0.86 (N 0.7-1.00 mmol/L). Hepatitis screen showed the patient was not immune to both hepatitis A and B. Immunoglobulin levels: IgG 15.2 (3.5-12.4 g/L). IgA 2.27 (N 0.4-1.2 g/L), and IgM 1.09 (N 0.43-1.7g/L), a picture of high IgG and IgA due to chronic infection. Screening for both parents by hemoglobin electrophoresis showed both of them had sickle cell trait. Sweat chloride test by the quantitative method (Wescor, USA) were positive in two occasions with 106, and 104 (N < 40 mmol/L). Urinalysis was normal, random urine sample showed a picture of hypercalciuria and hyperuricosuria. Ca level 0.78 mmol/L, uric acid 2.89 mmol/L, Creatinine (Cr) 6 mmol/L, and oxalate level 0.45 mmol/L. Sputum culture grew staphylococcus aureus that is resistant to Penicillin, but sensitive to Augmentin, Cefzolin and Cloxacillin.

Chest X-ray showed mild peribronchial wall thickening, otherwise within normal limit. Barium swallow showed intermittent Gastr-esophageal

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reflux. Computerized (CT) scan of sinuses showed opacities involve bilateral maxillary and ethmoid sinuses. MBG scan of 99m technetium DMSA scan showed normal out line in all aspects of the renal cortex bilaterally with differential function of left (Lt) 48.7 and right (Rt) 51.3%. Screening for Cystic fibrosis transmembrane regulator gene mutations (CFTR) showed the presence of the two pathogenic mutations; Novel Arab mutation H139L in exon 4 in the first allele and S549R mutation in exon 11 in the other allele (compound heterozygous).

The patient was treated with IV hydration, IV ceftriaxone for 10 days and IV Morphine as a pain medication. The patient markedly improved and was sent home with proper education for both diseases and pancreatic enzymes, multivitamins, Bacterim prophylaxis, Folic acid, Hydrochlorothiazide as diuretics to improve hyperuricosuria and inhaled Salbutamol and Becotide 2 times/day. Six months later the patient was admitted to hospital with a history of loud snoring, an obstructive apnea. X-ray of lateral neck showed large adenoids that is obstructing the nasal passage. The patient had tonsillectomy and adenoidectomy with marked improvement of the clinical picture.

Sickle cell anaemia and cystic fibrosis are diseases with autosomal recessive inheritance. Since the  $\beta$ -globin gene cluster is on chromosome 11 and the cystic fibrosis transmembrane regulator (CFTR) gene is located on chromosome 7, there is little likelihood of linked inheritance under normal circumstances. The chances of these diseases coexisting in a person of black ancestry can be estimated to be  $(\frac{1}{625}) \times (\frac{1}{14,000}) = (\frac{1}{8,750,000})$ , or  $1.14 \times 10^{-7}$ <sup>[1]</sup>. This calculation assumes both diseases are inherited in an autosomal recessive pattern in which both parents contribute an abnormal allele for sickle cell disease and cystic fibrosis to the child.

If this theory applied to our case, based on the incidence of both diseases in Saudi Arabia is accepted, the incidence of CF/SS in one patient would be in the range of  $(\frac{1}{4243}) \times (\frac{1}{137}) = 1/581,291$  live birth, i.e. it will be a rare disease.

There have been three previous reports of patients with the combination of sickle cell anaemia and cystic fibrosis. Amendola et al.<sup>[7]</sup> reported a 9-year old black child with cystic fibrosis and a variant form of sickle cell anaemia, hemoglobin S-D disease. This child was started on a transfusion regimen at 1 year of age because of rapidly progressive pulmonary disease; her pulmonary disease at the time of publication was comparable to other children her age with cystic fibrosis alone. Porter et al.<sup>[8]</sup> recorded the cases of two black children (22 months and 7 years old) with cystic fibrosis and sickle cell anaemia (hemoglobin SS disease); neither seemed to have experienced an exacerbation of one disease that affected the other. In these three cases, as in our patient, the haematological disease did not exacerbate the course of pulmonary disease, once the haematological problem was recognized and

treated. In addition, the haematological disease did not worsen the course of cystic fibrosis pulmonary complications. The third report<sup>[1]</sup> was of an adolescent of black and Hispanic ancestry from the Dominican Republic with both diseases. This patient had normal pulmonary function test and was stable on Cephlexin prophylaxis and inhaled albuterol with no apparent complication<sup>[1]</sup>.

The unusual co-occurrence of sickle cell disease and cystic fibrosis prompts speculation about the pathophysiologic effects and treatment of both diseases in one child. Does the presence of sickle cells disease ameliorate or worsen the course of cystic fibrosis? How does cystic fibrosis affect the course of sickle cell disease? None of the previous four cases, mentioned in the literature, seem to have had any ill effects from this combination. Collaborative efforts between paediatric haematologists and paediatric pulmonologists will be needed to find enough patients to answer these questions.

The incidence of both diseases to be seen simultaneously in the same patient will be in the range of 1/0.5 million live births in Saudi Arabia.

## SUMMARY

Combination CF/SS disease is a rare phenomenon in Saudi Arabia. Awareness of existence of both diseases should be increased, since SS disease is seen very frequently in pediatric clinic, and screening for co-existence with CF should be raised especially in patients with SS disease and repeated chest infection. Co-existence of both diseases may not change the course of the disease, but the patient needs multiple medications and close follow-up.

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