Case Report: A Nigerian Child with a diagnosis of cystic fibrosis – Review of literature and challenges with management in a resource-limited setting

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ABSTRACT:

Cystic fibrosis, an autosomal recessive disease that arises from a defective cystic fibrosis transmembrane conductance regulator (CFTR) protein is not a common genetically inherited condition recognized among people of non-Caucasian or African descent and is sparsely reported in the literature from sub-Sahara Africa. The presentation of Cystic fibrosis in a Nigerian child with no history of parental consanguinity or foreign ancestry has not been reported. Herein, we report a case of a 4-year-old Nigerian male who presented with classical clinical features of Cystic fibrosis that was confirmed following genetic testing and also highlights challenges with management in a resource-limited setting.

Keywords: Cystic fibrosis, Paediatrics, Genetic study, Nigeria, Case report.

INTRODUCTION

Cystic fibrosis (CF) is a chronic and often debilitating disease affecting predominantly the respiratory and digestive tracts. It arises from a mutation at position 7q31.2-q31.1 of the 7th chromosome which causes a defective cystic fibrosis transmembrane conductance regulator (CFTR) protein[1]. This incurable, autosomal recessive condition is not recognized as a common genetically inherited disorder among people of non-Caucasian or African descent and is sparsely reported in the literature from sub-Saharan Africa. However, the under-reporting may not be unrelated to a paucity of diagnostic facilities within the continent and insufficient awareness of the disease[2]. Although, CF is known to abound in Europe, few studies conducted in Northern and Southern Africa[3,4] suggests the possibility of population-specific CF mutations since most identified mutations in the CFTR protein, vary widely. However, the finding of CF even among

black children remains uncommon. Herein, we report the case of a Nigerian male who was born in the United States of America with no history of parental consanguinity or foreign ancestry who initially had a newborn screening (NBS) done but was lost to follow-up and subsequently presented to a tertiary hospital in South South Nigeria with classical symptoms of CF. The challenges of management and follow-up are discussed and this report is aimed at creating awareness among health care providers to consider CF in children presenting with features a chronic history of malnutrition with or without malabsorption and chronic lung disease.

CASE REPORT

A 4years old boy presented to the children outpatient clinic with complaints of progressive abdominal swelling, passage of fatty bulky stools and poor weight gain of 2 years duration, recurrent cough of 5 months duration, catarrh, difficulty breathing of 3 weeks duration and fever of 2 days. Abdominal swelling was generalized and progressively increased in size, worsened by feeding with associated abdominal discomfort. Stools were pale and butter-colored, very oily such that the oil can literarily be scooped from the stools as described by mother. His bowel opening was 3 to 4 times daily and he had a protruding rectal mass after defecation which was reducible and bled occasionally. Cough was non-paroxysmal, productive of yellowish sputum, distressful, associated with post tussive vomiting. He also had nasal congestion with thick yellow-coloured nasal discharge. His fever was high grade and intermittent. A review of systems showed that he had a history of forming salty crystals on the body after episodes of profuse sweating outside of an air-conditioned room.

Pregnancy was desired, uneventful and conception unassisted, it was initially supervised at the Rivers State University Teaching Hospital, Port Harcourt, Nigeria. The child was, however, born in a hospital in Houston Texas, USA with a birth weight was 3.17kg.

He had a newborn screening (NBS) performed on the 2nd day of life and was found to be positive for cystic fibrosis. He did not have any follow-up hospital visits due to his mother's misunderstanding of the NBS test results. At 2 months of age, he was brought back to the hospital of birth where his parents reported he developed thick catarrhal discharge and cough with difficulty breathing. He was subsequently admitted, and nebulized, received intranasal oxygen, parenteral antibiotics, commenced on pancreatic enzyme replacement therapy (Creon) and multivitamins, and was discharged home. He returned to Nigeria at 5 months of age. Since his return, his mother had stopped nebulization as she said she did not know that his medications were to be long-term.

He is the second of four children, three males and a female, of non-consanguineous Nigerian parents, of the Hausa tribe with no known Caucasian ancestry. There was a positive maternal history of 2 previous mid-trimester miscarriages.

On examination at presentation, he was small for his age with thin limbs, had grade 3 digital clubbing (Fig 1), and several non-tender submandibular, cervical lymph, and axillary lymph node swellings, no pedal oedema bilaterally.

His weight (12.5kg) was at the 0.58th percentile for his age (-2.5 Z scores), SPO_2= 79% in room. His respiratory rate was 32cycles per minute and rhonchi were heard on auscultation, pulse was 110bpm, full volume, regular and synchronous, blood pressure was 90/50mmHg, heart sounds S1 and S2 only were heard. Other systemic examinations were unremarkable. A clinical diagnosis of Cystic Fibrosis with bronchiectasis and failure to thrive, reducible rectal prolapse was made to rule out Pulmonary tuberculosis and malabsorption syndrome.

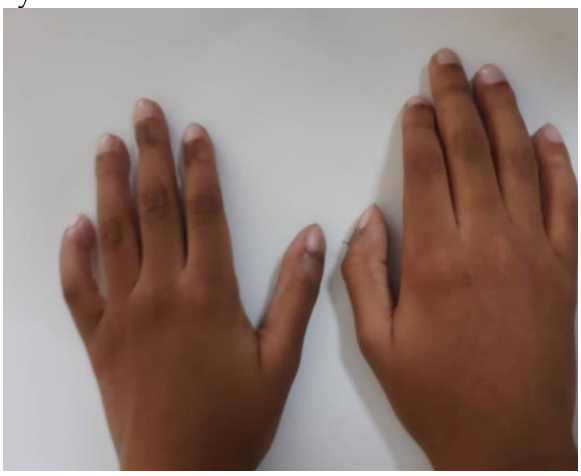

Fig 1: Digital clubbing grade 3.

DIAGNOSTIC ASSESSMENT

His sputum culture grew *Staphylococcus aureus,* sensitive to ceftazidime, ceftriaxone, gentamicin, Erythromycin, and ofloxacin. Chest X-ray that was done revealed interstitial shadowing in the upper, middle lung zones with accentuations of broncho-vascular markings in keeping with interstitial pneumonitis (Fig. 2). Abdominal ultrasound showed enlarged liver of 14.3cm with atypical homogenous parenchymal echo patches. Genetic testing was done after counselling the mother on the need for a confirmatory test since we did not have access to any past hospital records. The test confirmed CF with 2 heterozygous, pathogenic gene variants: Exon 14, c.2215del (p. Val739Tyrfs*16) and Exon 23, c.3764C>A (p.Ser1255*) and one variant of uncertain significance (Exon 22, c.3607A>G (p.Ile1293Val) in the Sequence analysis and deletion/duplication testing for protein transmembrane conductance regulator (CFTR). We were, however, unable to do faecal elastase level. Spirometer done at six years-of-age, that is two years into his follow up showed increased FVC, (203% of predicted), decreased FEV1/FVC% (46.8%) and FEF2575 (23.2%) in keeping with obstructive lung disease with air trapping.

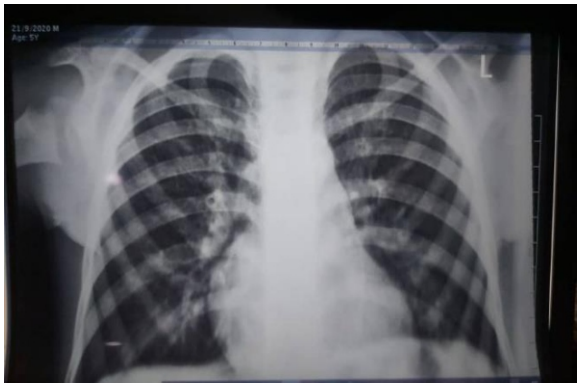

Fig 2: C Xray showing, interstitial shadowing in the upper, middle lung zones with accentuations of broncho vascular markings.

Therapeutic Intervention

He was commenced on twice-daily nebulization with 2.5mls salbutamol and 3mls of normal saline, followed by chest physiotherapy with postural drainage after nebulization. The lower respiratory tract infection was treated with 1 week of

erythromycin. Pancreatic enzymes medications were prescribed which took a month for him to begin the replacement therapy since it had to be imported into the country. He also commenced multivitamins (ABIDEC). Intermittent rectal prolapse was managed conservatively with sitz bath and witch-Hazel astringent pads PRN. He was referred to a dietician, and counselled, on the likely course of the disease, the need for continued strict adherence to prescribed supplements, and the significance of the CFTR genetic test results.

Follow Up and Outcome

Two years into his follow-up, he has been generally stable, evidenced by an increase in weight for age from 5th to 13th percentile (18kg), he has not had chest infections, his stools are less fatty and his baseline SPO_2 in room air has improved from 79% to 98%. He is still being followed up in the Respiratory clinic and procurement of pancreatic supplements is still from outside Nigeria.

TREATMENT CHALLENGES

His medications were being procured by the parents and were ordered from the USA and UK. Father pays out-of-pocket for each pack of Creon and averagely procures 12 packs per order which should on the average get exhausted after 4 weeks. Each pack costs ₦ 35,000.00 (£60.00). Strict compliance to the use of pancreatic lipase supplements was not possible as it depended on its availability. The ideal choice of mucolytics was also not available in the country and we had to use nebulized normal saline. Also, the confirmatory genetic testing was done in a laboratory based in the United States of America, thus increasing the overall cost of the test to accommodate shipping and handling charges. Additionally, there was the prolonged time interval from the time of sample collection to retrieval of results that took 6 weeks.

DISCUSSION

This is a case of cystic fibrosis (CF) in a Nigerian child. Cystic fibrosis is the most common autosomal recessive disease that causes early mortality among Caucasians[5]. It was initially reported to affect only Caucasians with a mutation detection rate of ≥ 95% reported in five European countries[3]. Recent research has shown that CF is also present in non-Caucasian populations including the middle east and Africa, although South Africa, Tunisia and Algeria were the only countries in which previous reports were available[3,6]. The authors did not find any literature that reported CF in a Nigerian child, implying that among the Nigerian population, it is rarely seen or has not been reported. As a result, reporting this case of CF in a child born of Nigerian parents with no known foreign ancestry would sensitize clinicians practicing in Nigeria not to completely disregard CF as a possible diagnosis.

Our patient presented with classical symptoms of CF, with recurrent respiratory infections, progressive abdominal swellings, rectal prolapse, frequent bulky, oily, stool, and poor weight gain. In CF there is a genetic defect that leads to the dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) protein[7]. The CFTR functions as a cyclic adenosine monophosphate (cAMP) regulated

chloride channel and it is located at the epithelial lining of the airways, biliary tract, pancreatic duct, intestine, sweat ducts, and vas deferens. Abnormality of chloride transport results in a decrease in chloride secretion, and an increase in reabsorption of sodium and water causing a decrease in fluid secretion while the protein portion of the secretion would become more viscid with the potential to precipitate and cause obstruction or a more viscous mucus that is difficult to clear in secretions from the respiratory system, gastrointestinal tract, pancreas, sweat gland and other exocrine glands[8]. The viscous mucus is also more adherent to bacteria which would promote infection and inflammation [9].

The clinical manifestation of CF is multisystemic. Gastrointestinal system manifestations include meconium ileus at birth which could present with progressive abdominal swelling, failure to pass meconium, and signs of intestinal obstruction. Older children like our patient can present with, intussusception, failure to thrive, and rectal prolapse. Rectal prolapse as seen in our patient occurs in patients with CF due to intestinal dysmotility which leads to straining with constipation that forces the anterior wall of the upper rectum into the anal canal such that over time the rectal attachments to the bony sacrum loosen leading to prolapse[10,11]. Symptoms of rectal prolapse also resolve with the commencement of pancreatic enzymes[10,12]. Pancreatic insufficiency leads to malabsorption of mainly fat and protein, with deficiency of fat-soluble vitamins, steatorrhea, anorexia, and recurrent abdominal pain. Some of these symptoms suggestive of pancreatic insufficiency were also present in our index patient. Involvement of the hepatobiliary system could cause jaundice and gastrointestinal tract bleeding. In the Respiratory system, a chronic or recurrent cough, prolonged symptoms of bronchiolitis, dyspnea on exertion, chest pain, recurrent sinusitis, nasal polyps, and hemoptysis with long-term complications of atypical asthma, pneumothorax, hemoptysis, and digital clubbing may be present. In the urogenital system, undescended testis, infertility especially in males due to the absence of vas deferens and delay in secondary sexual characteristic development are possible features[8,9].

DIAGNOSIS

Diagnosis of CF can be suspected from clinical symptoms or positive family history. While in many countries in Europe and other countries with significant number of European ancestries[13], neonatal screening is routinely done as part of their national policies. Neonatal screening for CF involves the blood measurement of immune-reactive trypsin (IRT) and pancreatitis-associated protein (PAP) which are both increased due to perinatal pancreatic damage[14-16]. Newborn screening programs allow for early diagnosis and prompt interventions which improve outcomes in CF patients. Confirmatory diagnosis is done by a sweat test or genotyping. Genotyping that shows 2 CFTR mutations in the presence of clinical symptoms is diagnostic of CF. Our patient had two mutations known to cause CF, he also had one more mutation of the CF gene, although this mutation seemed to be a

private mutation whose impact has not been fully studied. The presence of private mutations in CF genes which usually run-in families is not uncommon[8]. The pathogenic gene variant c.2215del (also known as c.2347delG) found in our patient was similarly reported by Ooi and Durie[17] to be among the common variants associated with pancreatic insufficiency in patients with CF. Also, the second heterogenous pathogenic gene variant (p. Ser1255*) was similarly documented among the CFTR mutations in black patients in the US[18]. Unlike the mutations found in our patient, a study among 123 CF children in Tunisia[2] found the Phe508del and E1104X mutations were the most common in their cohort. Our finding also differed from the 3120+G A and D1270N mutations reported among Southern African blacks with CF[19] as well as the A141D, L227R, and N1303H mutations reported in Algeria[4].

Sweat test involves the iontophoresis of pilocarpine into the body through the skin to stimulate sweating. The secreted sweat is then collected in a pre-weighed filter paper which is protected from evaporation and contamination. The sweat is then collected from the paper and analyzed for chloride, sweat chloride levels of >60meg/L are confirmatory of CF[8,14]. Sweat test requires experienced personnel and the samples need to be handled carefully, also laboratories that have proficiency for analyzing it are usually designated CF laboratories, given all these limitations we could not do the sweat test for our patient, as no such reference laboratories are within our locale. There was also evidence of lung disease in our patient with *Staphylococcal* lung infection and chest x-ray findings of interstitial lung disease. The lungs of children with CF are found to be normal at birth but they soon acquire lung infections that are difficult to eradicate[8] common organisms that are implicated include enteric organisms, *Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae.* The first manifestation of CF in the lungs of children is usually as small air way disease[20], this could explain why the Predicted FEF2575 of our patient was the most severe abnormal spirometer index at 23.2%. Chronic obstructive lung disease with air trapping seen in our patient is also in keeping the pattern of lung disease seen in children with CF.

MANAGEMENT

Management of CF involves a multi-disciplinary team approach. The patients need proper counselling and health education on the disease, the importance of which cannot be overemphasized as seen in our patient whose mother was not initially aware of the long-term care needed for her child till later. The goal of management is to maintain lung function, ensure adequate nutritional balance and manage complications of the disease[9]. Lung function is maintained by controlling respiratory infections and clearing the airways of mucus through the use of inhaled bronchodilators, followed by chest physical therapy and postural drainage. Mucolytics like Dornase alfa and nebulized hypertonic saline are used, although due to unavailability our patient used only normal saline which is not as effective as hypertonic saline. Nutritional therapy is achieved by the use of pancreatic enzyme supplements, fat-

soluble multivitamins, and minerals to maintain growth. All of which our patient was able to have. Diet should also include high energy, high-fat meals with additional salt intake, especially in hot climates to make up for the salt loss during exercise and sweating. Newer medications that potentiate or correct CFTR help to reverse the abnormality in chloride transport include; Ivacaftor, lumacaftor, and Elexacaftor[21,22]. Antibiotics are also indicated to treat persistent chest infections, while regular exercises especially upper body exercises like paddling are recommended to develop respiratory muscles. Complications of CF include liver diseases and diabetes mellitus which would require insulin. Other complications that could require surgical intervention include pneumothorax, nasal polyps, persistent chronic sinusitis, meconium ileus, intussusception, rectal prolapse, and end-stage lung disease for which lung transplant would be indicated[23].

Our patient has had remarkable improvement in his symptoms two years into follow-up, with improvement in his quality of life. The road ahead is still very difficult as CF is a chronic multisystemic condition that requires long-term interventions some of which are difficult to access in Nigeria.

CONCLUSION

Cystic fibrosis is still very rare in Nigeria but a high index of suspicion should be entertained especially in patients presenting with a chronic history of malnutrition with or without malabsorption and chronic lung disease. Management of CF in Nigeria needs international collaboration to provide the resources needed for its diagnosis and treatment. With adequate health education, medical treatment and follow up, quality of life and survival can be improved for patients living with CF in Nigeria.

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