CASE REPORT

Tetralogy of Fallot coexisting with sickle cell anaemia in a Nigerian child: course, complications and review of the literature

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Abstract

Tetralogy of Fallot (TOF) is a cyanotic congenital heart disease (CCHD) characterized by hypoxemia, cyanosis, and compensatory polycythaemia. Sickle cell anaemia (SCA) is a genetic disorder of the red cell haemoglobin characterised by recurrent erythrocyte sickling, haemolytic anaemia, and vaso-occlusive crises. Both are associated with significant morbidity and mortality and when they co-exist, complications are additive with poor outcomes. We report a fatal case of a 9-year-old boy diagnosed with SCA at seven months and TOF at age six despite having features suggestive of cardiac disease since infancy. He remained clinically stable (without hypoxic spells or sickle cell crisis) until age 8 when he had severe sepsis with malaria and anaemia warranting Intensive Care Unit (ICU) management. He presented a year later at the emergency unit with acute fever and altered level of consciousness and died within a few minutes of presentation. This case has brought to the fore that cyanotic heart disease such as TOF could coexist with SCA, and the outcome is fatal. A high index of suspicion is thus crucial to early diagnosis and improved outcome.

Keywords: Tetralogy of Fallot, sickle cell anaemia, co-existent, child, outcome, Nigeria

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic CHD and accounts for 7 to 10% of CHD.[1] It is characterized by reduced blood flow to the lungs for oxygenation and a right-to-left shunt of desaturated blood to systemic circulation. This results in hypoxemia, cyanosis, and compensatory polycythaemia due to an increase in erythropoietin production to maintain tissue oxygenation. Prolonged hypoxemia and polycythaemia can result in organ damage.[1]

Sickle cell anaemia is a genetic disorder (haemoglobinopathy) of the red cell haemoglobin (Hb) characterised by recurrent hypoxia-induced red cell sickling, haemolytic anaemia and vaso-occlusive crises which results in widespread organ damage and early mortality in childhood. The greatest burden of sickle cell disease (SCD) is in sub-Saharan Africa where about 300,000 children are born annually with this condition. About 50-80% die before their fifth birthday. Nigeria has the largest pool of people with SCD with about 150,000 births annually.[2]

The genetic mutation is in the β-chain of the Hb where fat-soluble amino acid valine replaces water-soluble glutamic acid leading to Hb S formation. Sickled haemoglobin (HbS) is insoluble under low oxygen tension and consequently deforms the red cells and becomes rigid leading to microvascular occlusion. Cardiovascular abnormalities in SCA, include cardiac enlargement, acute stroke, chronic cerebral ischemia, arrhythmias, increased arterial stiffness, and micro-circulation damage.[3] Polycythaemia in CCHD leads to hyperviscosity and when CCHD coexist with SCA, the presence of deformed and rigid RBC could worsen the microvascular occlusion and increase the risk of vascular accidents.[4]

There has not been any report of co-existent cyanotic CHD and SCA in Nigeria. Available reports elsewhere were associated with severe symptoms and dismal outcomes.[5-7] This report highlights the challenges of this double pathology in a resource-constrained setting.

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Ethical statement

This case study was approved by the ethical review committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto with approval number UDUTH/HREC/2021/1034/V1. The parents provided written consent for the publication of clinical details after they received comprehensive information. They were assured that their child's identity would be protected.

Case report

A 9-year-old boy was first diagnosed with SCA in infancy (at the age of seven months) and then TOF when he was 6 years old after an incidental finding of cardiac murmur and cardiomegaly were noticed during a respiratory infection. There was a history of recurrent fast breathing on exertion and easy fatiguability since he was 14 months old. The suck rest cycle occurred in early infancy but no cyanosis. There was no history of spells or squatting. He was relatively stable and free from painful and anaemic crises and had never been transfused.

Pregnancy, labour, delivery, and perinatal events were uneventful. He was the second of four children. There was no history suggestive of cardiac and SCD in siblings. Both parents were carriers of sickle cell trait and non-consanguineous.

Clinical findings at age six (first clinic presentation)

He was underweight (72% of expected) with mild stunting (91% of expected). He had no habitus of SCD. He was calm, not in respiratory distress, not pale, acyanosed with SpO_2 of 62% in room air and grade 3 digital clubbing. His precordium was not hyperactive nor bulging. The apex beat was in the fifth left intercostal space (LICS) with no heave or thrills. Heart sounds were first and second (single S2). He had a long ejection systolic murmur (grade 3) loudest at the second LICS. Respiratory, musculoskeletal, and neurological examinations were normal.

Diagnostic assessment at age six (at first clinic presentation)

Haemoglobin electrophoresis showed an SS phenotype confirming SCA. The full blood count (FBC) showed leucocytosis with lymphocytic predominance (Table I). Also, the haematocrit was lower than the expected compensatory polycythaemia in a cyanotic patient. All the red cell indices were lower than normal, and the red cell distribution width was high supporting possible iron deficiency. Haemoglobin quantification by high liquid performance chromatography (HPLC) and iron studies was not done due to financial constraints.

Chest radiograph features included oligemic lung fields and right ventricular hypertrophy with an upturned apex. Cardiothoracic ratio was 0.54. (Figure 1). Electrocardiogram indicated tachycardia, right axis deviation of the QRS complex and right ventricular hypertrophy (Figure 2). Echocardiography revealed features of Tetralogy of Fallot which were large non-restrictive ventricular septal defect (VSD), overriding of aorta, infundibular stenosis, and right ventricular hypertrophy (Figure 3). There was also severe right ventricular outflow tract (RVOT) obstruction with a peak gradient of 38.5 mmHg.

Course, complications, and outcome

He was commenced on oral Propranolol to prevent infundibular spasms and cyanotic spells while he continued his routine hematinics, anti-malarial and antibiotic prophylaxis. Follow-up was commenced at both the Paediatric Cardiology and Sickle Cell Clinics. The caregivers were counselled about the double pathology in the child. However, they felt the child was relatively stable and defaulted from follow-up. They were also counselled on the need for surgical intervention for the CHD but could not afford it.

Two years later, he developed an acute febrile illness with convulsions and altered consciousness. He was severely pale (HCT=7%), SpO_2 was 11% in room air with blood pressure 75/40mmHg. He was managed in the ICU for hypoxic spells from sepsis and severe malaria with severe anaemia. He was commenced on mechanical ventilation-SIMV mode (synchronized intermittent mandatory ventilation) under anaesthesia. The oxygen saturation subsequently improved to 91 – 95% while the blood pressure improved to 92/40mmhg. He was discharged from intensive care to the ward after four days. He received parenteral antibiotics (Ceftriaxone, Ciprofloxacin), oral Clarithromycin and anti-malaria medications. However, fever, abdominal, and bone pains persisted. Urine analysis showed oxalate crystals and culture yielded Pseudomonas aeruginosa which was resistant to the antibiotics he was on but sensitive to Penicillin and Piperacillin. The blood culture was negative for any pathogen while renal function and abdominopelvic scan were normal. The full blood count done after the blood transfusion showed leucocytosis with lymphocyte predominance (Table 1). He subsequently responded to parenteral, and then oral Amoxycillin-

Table 1: Full blood count (FBC) results at first clinic consultation and during subsequent admission

Parameter	At diagnosis (steady state)	1st admission (for sepsis)	Normal range
White cell count (x 10^9/l)	13.7	38.3	4 – 11
Lymphocytes (%)	49.3	60.5	25 – 45
Neutrophils (%)	37.2	29.3	45 – 55
Eosinophils/basophils/monocytes (%)	13.5	10.2	0 – 4
Red cell count (x10^9/l)		4.02	4.55
Haematocrit (%)	29.2	31.0	32 – 44
Mean corpuscular volume (fl)	78.9	76.7	80 – 95
Mean corpuscular haemoglobin (pg)	22.7	23.8	27 – 31
Mean corpuscular haemoglobin concentration (g/dl)	28.8	31.0	32 – 36
Platelets (x10^9/l)	218	278	150 – 400
Red cell distribution width (%)	28.8		11.5 – 14.5

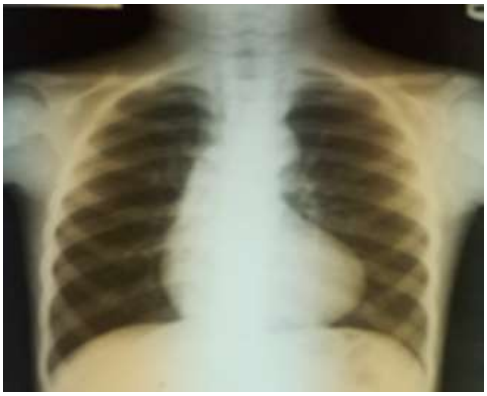

Fig 1: Chest x-ray showing upturned apex and oligaemic lung fields.

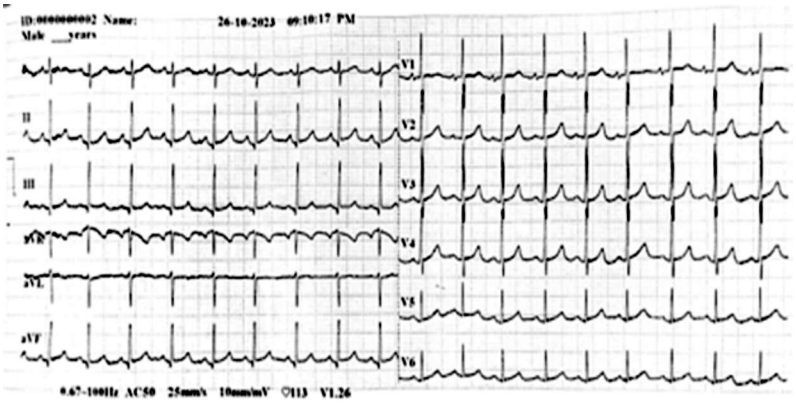

Fig 2: ECG showing right atria (Tall P waves) and right ventricular enlargement (dominant R wave in V1

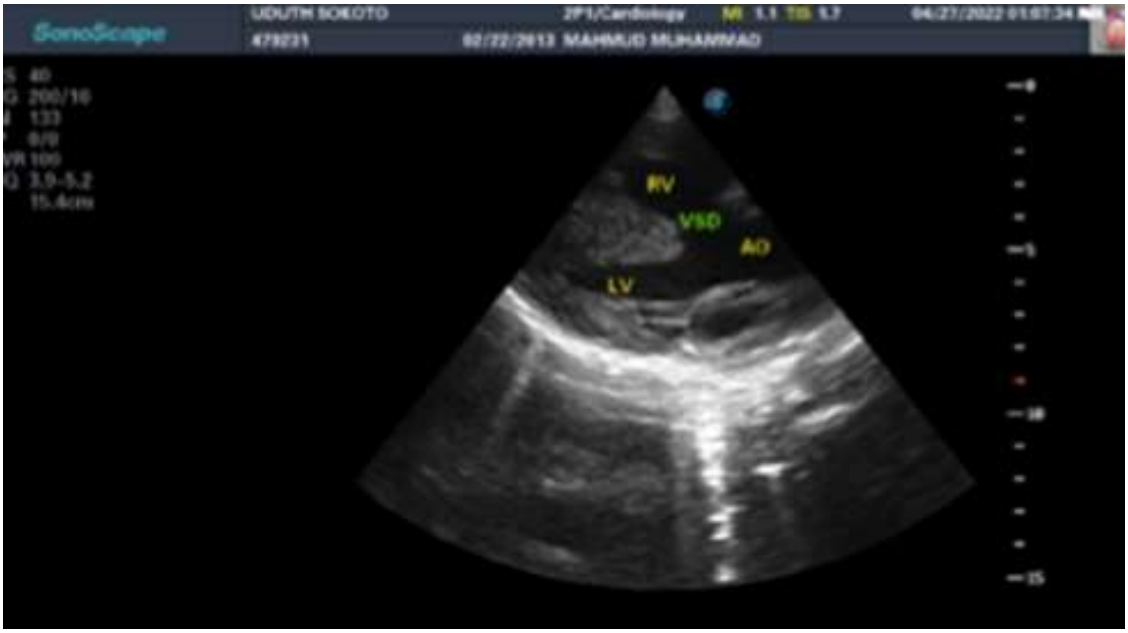

Fig 3: Echocardiographic image showing large non-restrictive VSD and overriding of aorta

clavulanate and was discharged after 3 weeks of hospitalization. Post-hospital discharge, the patient defaulted to clinic follow-up. About a year later, he had a repeat episode of severe illness characterized by a one-week history of high fever and an altered level of consciousness. He died within a few minutes of presentation at the Emergency unit.

Discussion

Most cases of coexistent SCA with CCHD like TOF were reported over four decades ago. Also, almost all cases were outside the African subcontinent despite the high burden of SCA.[5,6,8] While this suggests the rarity of the coexistence of the diseases especially among blacks, it is also possible that cardiac diseases were undiagnosed given the grossly inadequate facilities for diagnosing CHD in most African settings, Nigeria inclusive.[9] The diagnosis of CHD was delayed in the highlighted case and was made only after presenting to a tertiary facility despite having suggestive signs of a cardiac disease since early infancy. This further suggests limited capacities for early diagnosis in our setting.

The initial stable condition of our patient could probably be due to the coexistence of the two diseases. The hypoxia-driven erythropoiesis caused by the cyanotic heart disease probably compensated for the increased red cell destruction by the haemoglobinopathy leading to the absence of anaemic crises. The rapid haemolysis associated with sickle cell anaemia also makes polycythaemia and perhaps hypoxic spells rare as evidenced in the index case. Also, the highlighted case had no prior vaso-occlusive crisis, and this may have been due to elevated foetal haemoglobin which has anti-sickling properties. Although foetal haemoglobin was not quantified in the index case, high levels of foetal haemoglobin in early childhood have been reported in a child with SCA and may have been the case in our patient.[12] Furthermore, he was not visibly cyanosed in the presence of significant desaturation. O'Keefe reported that the absence of visible cyanosis despite significant desaturation is because clinical cyanosis is not reliable in the setting of anaemia warranting pulse oximetry assessment.[6]

The patient has laboratory parameters consistent with iron deficiency anaemia i.e., low MCH and MCV and high than red cell distribution width. Higher iron levels have been noted among patients with SCA largely due to frequent transfusions and chronic haemolysis. However, iron deficiency may have resulted from the coexisting cyanotic heart disease.[10] Iron deficiency anaemia is known to aggravate hyperviscosity symptoms due to the presence of less deformable microcytic erythrocytes microcirculation.[4] The index patient was however stable until he was eight

years old. It is uncertain when he became iron deficient because his haematological profile was hitherto unknown. Perhaps the onset of severe symptoms coincided with the onset of iron deficiency anaemia.

Unlike the index case, the onset of cardiac symptoms was early in previous reports. O'Keefe reported a male infant with TOF and SCA who had spells from the second months of life and other cardiac symptoms from the age of 18 months warranting several admissions and hospitalization.[6] In another report, a girl with glucose-6-phosphate dehydrogenase deficiency (G6PD) in addition to TOF and SCA developed anaemic symptoms at the age of 3 months. The coexistence of G6PD deficiency (a known cause of haemolytic anaemias) may have aggravated the anaemia and hence the early presentation.[11] Also, Venugopal and colleagues reported a case of a year-old boy with TOF and ß-thalassemia major who had recurrent hypoxic spells from the age of six weeks. The patient, however, had successful surgical repair of the heart lesion, unlike the index case.[7] β-thalassemia major is a known cause of microcytic anaemia due to decreased production of the haemoglobin chains and as such may potentiate microvascular obstruction and spells.[4]

Tetralogy of Fallot has been described in this report; however, other forms of congenital cardiac anomalies coexisting with SCA have been described in the literature. Iannucci[5] described varying complex congenital heart diseases i.e., hypoplastic left heart syndrome, Transposition of great arteries (TGA) and double inlet ventricle with pulmonary stenosis in five children with SCA. Like the index case, outcomes of the patients were poor with recurrent cerebrovascular accidents (in three), childhood death (in four; aged 12 months to 17 years) and ventricular dysfunction in the survivor despite an early diagnosis of the CHD and cardiac surgery. Similarly, coexisting TGA has been reported. The patient had a recurrent stroke and ultimately died at age three.[12]

Both SCA and CCHD are prone to bacterial infection. Although the blood culture was negative, Pseudomonas was isolated in the urine during the initial hospitalization. Subjects with SCA are known to be prone to infection by encapsulated organisms due to functional asplenia, increased bioavailable iron from recurrent haemolysis and tissue infarcts which could serve as a nidus for infection.[13] Cyanotic CHD especially the complex variants may also be associated with immunodeficiencies from thymic hypoplasia and hence, predisposed to infections.[14] Children with CHD have increased energy needs due to their cardiac condition and are frequently malnourished as seen in the index case and are thus predisposed to infection.

Conclusions and Recommendations

Cyanotic congenital heart diseases could be present in subjects with SCA, and the outcome is often fatal, especially in low-resource settings where diagnoses are delayed and capacities for corrective cardiac surgeries are not available. Clinicians should have a high index of suspicion of CHD in children with SCA rather than attributing cardiac murmurs and cardiomegaly to chronic anaemia alone.[6] Screening echocardiography should be considered as an essential investigation for children with sickle cell anaemia presenting with cardiac signs.[15] Also, family history suggestive of SCA should be explored and Hb phenotyping should be prioritised in children with CCHD who have suggestive history. In addition, stringent multidisciplinary follow-up should be instituted for affected patients. Furthermore, the need to improve the capacity of the healthcare system to provide definitive cardiac surgery cannot be overemphasized.

Competing interests

The authors declare no competing interests.

Authors' contributions

KOI conceptualised the report and wrote the initial draft.
UMS, UMW, BIG, BJ and NMJ reviewed the manuscript.
LKC and MAF contributed to the literature searches and patient care.

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