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RESEARCH ARTICLE

DESCRIBING ACUTE CHEST SYNDROME IN CHILDREN WITH SICKLE CELL ANAEMIA

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ABSTRACT

Acute Chest Syndrome (ACS) is a potential life threatening complication of Sickle Cell disease (SCD) characterized by the presence of new pulmonary infiltrates with respiratory findings in a patient with SCD. It is the second commonest cause of hospital admission in SCD, next to vasoocclusive crises and accounts for 25% of mortalities. The aetiology is unknown but infection and infarction play major roles. Common presenting features include fever, cough, wheezing, chest pain and pleural effusion. An abnormal Chest X-ray is generally required to confirm the diagnosis. The X-ray changes were previously thought to be caused mainly by infection but recent reports have suggested that pulmonary infarction due to local sickling and emboli may be more likely. Treatment includes intravenous antibiotics using a third generation cephalosporin and a macrolide or quinolone, blood transfusion, hydration and analgesics. NSAIDs may worsen ACS due to vasoconstriction and bronchospasm, corticosteroids are controversial, bronchodilators may be useful, Nitric oxide (NO) has been found to be beneficial and bronchoscopy is not routinely done. Because ACS is common in children and yet often underdiagnosed, all paediatric SCD patients who present with fever should be evaluated with a chest radiograph and daily fluid intake should not exceed 1,500mls/m^2/day. The aim of this report is to add to the understanding of ACS in this region and also to sensitize physicians to the spectrum of clinical presentation of ACS so as to improve diagnosis and treatment and hence prevent morbidity and mortality.

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INTRODUCTION

The term Acute Chest Syndrome (ACS) was first suggested in 1979 by Charache *et al* and had been developed to represent the peculiar nature of acute pulmonary illness in patients with Sickle Cell Anaemia (SCA) (Bernard *et al*., 2007). It is a rapidly occurring pulmonary disease characterized by lower respiratory tract symptoms, hypoxia and a new infiltrate on Chest X-Ray (CXR).(Miller 2011,Taylor *et al*., 2004,Crabtree *et al*., 2011,Claster and Vichinsky 2000). It is a leading cause of mortality in Sickle Cell Disease (SCD) (Claster and Vichinsky 2000) and the second commonest cause of hospital admission in SCA, next to Vasoocclusive Crises (VOC) (Gladwin and Rogers 2000, Paul *et al* 2011). SCD is a chronic inherited hematological disorder caused by abnormal haemoglobin of the B globin gene due to substitution of glutamic acid by valine at position 6 of the B globin polypeptide chain (Ballas *et al*., 2012). There are no firm data on incidence of ACS in Nigeria (Fawibe 2008), especially in children. The aetiopathogenesis of ACS is complex and not yet well understood, with two types of lung involvement existing in patients with SCA-ACS and Chronic Lung Disease (CLD) (Taylor *et al*., 2004, Crabtree *et al*., 2011, Paul *et al*., 2011, Fawibe 2008, Vichinsky *et al*., 2000). When known, aetiology is multifactorial and usually difficult to obtain but pulmonary fat embolism and infections are prominent factors (Bernard *et al*., 2007, Miller 2011, Taylor *et al*., 2004, Crabtree *et al* 2011, Paul *et al* 2011, and Vichinsky *et al*., 2000). The known causes of ACS are infection, pulmonary vascular occlusion (from pulmonary thrombosis, fat embolism and peripheral thromboembolism), hypoventilation/atelectasis (from thoracic bony infarction, abdominal pain and opioid use), pulmonary oedema (from intravenous fluids, opioids and pulmonary vascular injury) and others like bronchospasm. (Taylor *et al* 2004). Infections are mainly caused by chlamydia pneumonia, mycoplasma pneumonia, streptococcal pneumonia, staphylococcus aureus, parvovirus B19, respiratory syncytial virus and influenza A (Miller 2011). The distinction between infection and infarction is often very difficult because the two

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conditions co-exist, with infection predisposing to infarction and vice versa (Srair *et al*., 1995). Incidence is related to age with children 2-4 years having the highest incidence. It is associated with all sickle cell genotypes but occurs most frequently in homozygous sickle cell disease (Bernard *et al*., 2007). The risk factors for the development of ACS include high steady state leucocyte count, low steady state haemoglobin F, high steady state haemoglobin concentration and post operation (especially three days following surgery) (Bernard *et al*., 2007,Gladwin and Rodgers 2000).

The diagnosis of ACS in SCD is challenging to the physician (Taylor *et al*., 2004) and is very often delayed (Vichinsky *et al*., 2000). It is often clinical and so careful history and physical examination is very important. Tachypnea, dyspnea and asymmetry of breath sounds, persistent crepitations nearly always indicate acute chest syndrome (Miller 2011). The most common presenting symptoms in children are fever and cough with or without wheezing and chest pain (Taylor *et al*., 2004, Srair *et al*., 1995) especially in young children aged 2-4 years (Paul *et al*., 2011). Clinically, fever, cough, chest pain, pleural effusion, leukocytosis with multiple lobe involvement are common. Duration of clinical illness and radiological clearance of infiltrates can be prolonged to 10-12 days with an average of 3-7 days (Paul *et al*., 2011). Clinical examination is often misleading and inconsistent with normal physical examination often seen sometimes in the absence of fever and therefore not contributory (Taylor *et al*., 2004). Physical examination is unreliable in predicting ACS as it may be normal or reveal crepitations (Bernard *et al*., 2007). Pain usually precedes ACS and a single physical examination or radiograph may not be adequate for early diagnosis (Vichinsky *et al*., 2000). Diagnosis involves CXR- new infiltrate usually involving the lower lobes but any lobes can be affected. Multilobar involvement is common and effusion can be present (Bernard *et al*., 2007). An occasional patient may have all the signs and symptoms with no new infiltrate on CXR. Also if a previous radiograph is not available, the infiltrate in question is considered as new (Ballas *et al*., 2012). X-ray findings are isolated upper or middle lobe disease in children while adults have multiple lobe involvements affecting predominantly the lower lobes. Adults also have pleural effusions more frequently (Claster and Vichinsky 2000) and not associated with infections (Paul *et al*., 2011). The lower and middle lobes are more often affected than upper lobes in children and multiple lobar involvements carry a poor prognosis. Pulmonary infiltrate resolve quickly in children with ACS not associated with infection (Paul *et al*., 2011).

The success of management is determined by the experience of the attending individual or physician. Up till date, there is no established consensus among providers on the management of complications of SCD partly because of lack of evidences and differences in the experience of providers (Ballas *et al*., 2012). A review of treatment options to assist management will be useful to those who don't attend to children regularly (Miller 2011). Standardization of care results from both guideline +development and implementation efforts and improves clinical outcomes for patients with SCD who are at risk of ACS or who already have ACS (Crabtree *et al*., 2011). A high index of suspicion is needed in the diagnosis and commencement of early and prompt treatment. The emphasis of management is on supportive care-analgesia, treatment of infections, oxygen supplementation, careful hydration and blood transfusion. There is also need for further investigation of the use of hydroxyureas and niclosan especially in those with recurrent disease (Fawibe, 2008). Treatment is supportive with antibiotics, bronchodilators, incentive spirometry for those who can co-operate and early transfusion when necessary. Patients admitted for VOC should be considered to be in the prodromal phase of ACS and therefore monitored closely for its development and prompt treatment (Bernard *et al*., 2007). Management generally revolves around monitoring oxygen saturation, reticulocyte count, hyponatremia and diurnal deterioration as well as use of macrolide antibiotics, antiviral agents, hydration at maintenance rate but watching out for pulmonary oedema which may indicate transfusion associated acute lung injury. Blood transfusion treatment basically "dilutes out" sickled cells and improves oxygenation. It is found to be effective and adequate for most children with ACS and simply 7-13 mls/kg of packed cells is preferred unless the haemoglobin concentration is >9g/dl and a partial exchange transfusion is required (Miller 2011). Exchange blood transfusion is also useful and reduces pulmonary fat embolism but should be reserved for patients who are not sufficiently anaemic to accommodate simple blood transfusion. Corticosteroid therapy has been found to be controversial as it increases re-admission rates and length of hospital stay. Usually dexamethasone 0.3mg/kg 12hourly for 4 doses or Prednisolone 2mg/kg/day for 5-7 days are given (Bernard *et al* 2007). Infections are frequently and prominently precipitated by atypical organisms mycoplasma and chlamydia and therefore ceftriaxone and a macrolide are mandatory for antibiotic treatment (Claster and Vichinsky 2000). Incentive Spirometry prevents atelectasis and reduces hypoventilation, preventing the development of new infiltrates in patients admitted with pain. There are no studies on use of spirometry in ACS but its use every 1-2hrs is an important adjunct to treatment (Claster and Vichinsky, 2000).

Case report

Case 1, a 13 year old male known with Sickle cell anaemia diagnosed 3 years previously in University of Calabar Teaching Hospital (UCTH), Calabar and who had not been regular with clinic attendance and routine medications. He presented with high grade continuous fever of one week's duration, chest pain of 3 days and cough and difficulty in breathing of one day's duration. The chest pain was sudden in onset, sharp and worse with inspiration in. Cough was productive of yellowish sputum, with associated difficulty in breathing, wheezing and fast breathing. He was not known with bronchial asthma. He had completed all childhood immunizations and was currently doing well in secondary school.

He first presented to General Hospital, Calabar with a history of fever and difficulty in breathing. He was found to be quite ill, moderately to severely pale, dyspnoic, tachypnoic with a respiratory rate (RR) of 52 cycles/minute (c/min), Pulse rate (PR) of 126 beats/minute (b/min), dull percussion notes over the right lung middle zone with stony dullness over the right lower zone. Air entry was poor in these zones with associated

crepitations. A tender hepatomegaly was also noted. Packed cell volume (PCV) was 17.4% and oxygen saturation was 93% while on oxygen. A working diagnosis of Right sided pleural effusion secondary to pneumonia in a sickler was made. Heart failure was a possibility. A CXR showed homogenous opacity of right lower lobe with air bronchogram and obliteration of costophrenic angle. The upper and middle lobes show inhomogenous opacities. The left lungs had prominent vascular markings and mild basal haziness (Fig. 1a). He received antibioctics for one day and was referred to the UCTH for further management. When reviewed in UCTH, he was acutely ill-looking, moderately pale, jaundiced, and febrile with a temperature of 39.3^{o}C celcius, tachypnoic with a RR of 70 c/min, dyspnoic with flaring alae nasi and intercostal recession. Oxygen saturation was 75% in room air and 85% on oxygen. There was reduced chest expansion on the right lower zone with dull percussion notes in the right mid and lower zones and bronchial breath sounds over the right mid and lower zones and bilateral coarse crepitations in both bases. The PR was 140 b/min with S_1, S2 and S_3 gallop rhythm. The Blood pressure (BP) was 120/80mmHg with a MAP of 67mmHg.There was tenderness over the right hypochondium with a tender hepatomegaly of 5cm below the costal margin. A working diagnosis of Right lobar Pneumonia to rule out Acute Chest Syndrome in HbSS was made. PCV was 17%. A chest and upper abdominal ultrasound scan showed no pleural effusion but cardiomegaly, hepatomegaly and enlargement of both kidneys. Other investigations included Full blood count (FBC) which showed total WBC of 10.9 X10^{9}/l, neutrophils of 69%, lymphocytes of 25%, eosinophils of 6% and platelets of 468 X10^{3}/ul. Blood culture yielded no growth. Electrolytes and urea were essentially normal. Mantoux test read 0mm with negative sputum for Acid fast bacilli (AFB). The intravenous crystalline penicillin and gentamycin were continued and caps Azithromycin and salbutamol nebulization were added to treatment.

He was transfused with packed cells and analgesics were also given. His condition began to improve as oxygen saturation went up to 91-92% on oxygen, RR dropped to 40c/min, BP dropped to 100/60mmhg, PR reduced to 80b/min and the liver became non-tender and its size reduced to 2cm. But fever persisted and so penicillin was changed to ceftriaxone after excluding tuberculosis and malaria. He continued to improve and was fit for discharge.

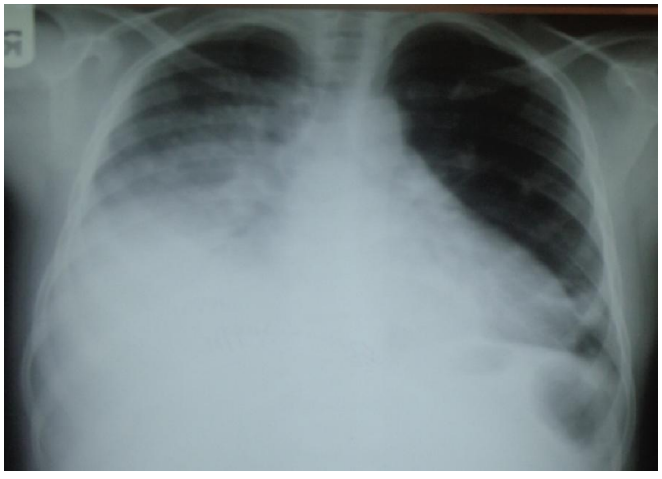

Figure 1a. Chest X-ray of Case 1 on admission

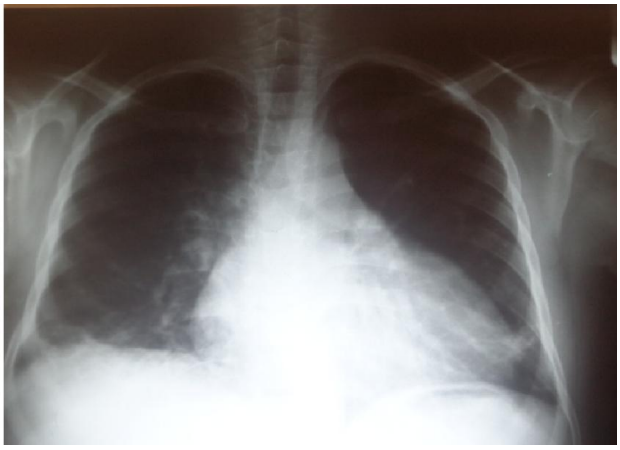

Figure 1 b. CXR of Case1 showing improvement

A repeat CXR showed interval improvement in chest signs with residual homogenous opacity on the right basal lobe and cardiomegaly (Fig. 1b). Heart failure was a possibility. The final diagnosis was acute chest syndrome with cardiomyopathy. Echocardiography and ECG done showed hyper dynamic circulation with mild RVH and LVH and no arrhythmias respectively. He was commenced on captopril tablets to continue daily folic acid and paludrine tablets and was discharged home after 11 days of admission with a PCV of 26%. Subsequent clinic follow up showed sustained improvement with subsequent resolution of all respiratory and cardiac signs.

Case 2, a 5 year old male known with sickle cell anaemia diagnosed 4 years before. He had been regular with his clinic follow up visits, taking daily folic acid, multivite and paludrin tablets, with a steady state PCV of 23%. He has received 2 or 3 doses of pneumococcal vaccine (prevenar-13) and has been transfused 3 times since diagnosis. He presented in the children's emergency unit following a referral from a private clinic. Symptoms were high grade continuous fever of 5 days duration and persistent non-productive cough of 3 days duration associated with difficulty in breathing, reduced appetite, vomiting and abdominal pains.

He had received ceftriaxone (Rocephin), gentamycin and artesunate during a 4 day admission in the private clinic. Physical examination revealed an ill looking boy, pale with a pcv of 17%, febrile with a temperature of 38.9^{o}C celcius, dyspnoic, tachypnoic with dull percussion notes on the right lower lung zone and a tender hepatomegaly. It was initially thought to be Pneumonia and so Cloxacillin was added to the treatment to cover for staphylococcus aureus. He was also transfused with packed cells. Further review considered the diagnosis of acute chest syndrome. A chest x-ray showed uniform opacification of the right lower lobe with preservation of pulmonary vascular markings, costophrenic and cardio phrenic angles and no air bronchogram. (Figure 2). The bones of the rib cage were normal. This was suggestive of right lower lobar infarction. FBC showed neutrophilia, and a blood film for malaria parasite was positive. He responded remarkably to the treatment with antibioctics and blood transfusion and was subsequently discharged home on oral Azithromycin to be

follow-up in the Paediatric outpatient clinic. He continued to improve with a normal physical examination and a clear chest.

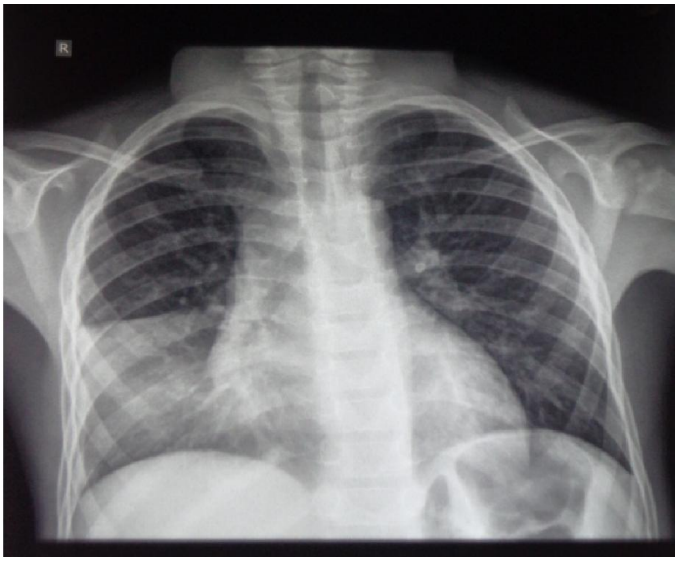

Figure 2. Case 2 on admission

DISCUSSION

Making the diagnosis of ACS did not come easy in the two reported cases as they were initially misdiagnosed as Pneumonia. This is in keeping with reports from studies which shows that the diagnosis of ACS in SCD remains challenging to the physician (Taylor *et al*., 2004) and is very often delayed (Vichinsky *et al*., 2000). Again, studies have documented the difficulties in distinguishing between infective pneumonia and ACS (Claster and Vichinsky, 2000).

The common presenting complaints in the two reported cases are fever, cough and difficulty in breathing, with Case 1 having chest pain, fast breathing and wheezing in addition. Several studies have reported common presenting features of ACS as fever, cough, chest pains, pleural effusions with multiple lobar involvement, singly or in combination (Bernard *et al*., 2007; Taylor *et al*., 2004; Paul *et al*., 2011; Srair *et al*., 1995). Case 1 first presented with pleural effusion which was transient.

The rapidity of resolution of the pleural fluid on the chest Ultrasound scan should have alerted a suspicion of ACS much earlier. Studies have shown that even though pleural effusions do occur in children (Bernard *et al*., 2007), they are more common in adults and are not related to infection (Paul *et al* 2011). Radiological clearance of infiltrates has been documented to be an average of 3-7 days with a range of 10-12 days (Paul *et al*., 2011). Both cases had mainly right sided middle and lower lobar involvement with some affectation of the upper lobe in addition in Case 1. Reports have shown that CXR shows affectation of lower and middle lobes more often than upper lobes in children (Paul *et al*., 2011).

The two reported cases responded to antibioctics, including azithromycin and blood transfusion. Case 1 benefitted from a bronchodilator nebulization in addition. This is in keeping with reported modalities of management being blood transfusion (Bernard *et al*., 2007, Miller 2011,Gladwin and Rodgers 2000, Fawibe 2008, Srair *et al* 1995) antibioctics including macrolides (Bernard *et al*., 2007; Miller 2011; Srair *et al*., 1995) and bronchodilator inhaler (Vichinsky *et al*., 2000). Both cases spent 11 and 4 days respectively on admission. Several other studies have reported average length of hospital stay as 4.1(Crabtree *et al*., 2011), 5.4(Bernaed *et al*., 2007) and 6.8(Claster and Vichinsky 2000) days.

Conclusion

Early identification, hospitalization and prompt treatment of all cases of ACS is very important as it accounts for 25% of deaths across all age groups. There should be CXR done, with frequent monitoring of respiratory signs and pulse oxymetry of all SCD patients admitted with pain and fever, irrespective of the diagnosis even if there are no chest symptoms. Also, once ACS has been diagnosed treatment should include a macrolide antibiotic and cautious hydration. Physicians managing these children should therefore have a high index of suspicion and a low threshold for diagnosing ACS in patients with VOC especially when they develop respiratory signs and symptoms. This will go a long way to reduce mortality in this population of children.

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