Original Article

Pattern of chronic lung lesions in adults with sickle cell disease in Lagos, Nigeria

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Abstract

Background: The vascular response to recurrent tissue hypoxia and reperfusion following red blood cell sickling causes acute chest syndrome and chronic lung disease. The purpose of this study was to determine the pattern of chronic lung lesions and possible risk factors in sickle cell patients in lagos, Nigeria.

Methods: From July 2012 to April 2013, Pulmonary function test (PFT) and chest-x-ray were determined in 56 eligible patients with sickle cell disease. Full blood count, red cell indices, hemoglobin F level, oxygen saturation, liver function tests, lactate dehydrogenase and tricuspid regurgitant jet velocity were measured.

Results: The mean age of the patients was 22±6 years. The mean forced vital capacity was low (76.49%±16). Abnormal PFTs were restrictive lung lesion (53%), obstructive lesions (3.7%) and mixed lesions (11%). The vital capacity had negative correlation with the white cell count and platelet count while it had positive correlation with age. There were no significant differences when normal and abnormal PFTs were compared based on the following laboratory data: lactate dehydrogenase (244 vs. 301), hematocrit (22.7 vs. 23.6), fetal hemoglobin (6.2% vs. 4.2%), mean corpuscular hemoglobin concentration (33.7 vs 33.3), aspartate transferase (34.2 vs. 35.1), tricuspid regurgitant jet velocity (1.3 vs. 0.92) and oxygen saturation (95.8 vs. 95.5). Abnormal x-ray findings were present in 84% of participants. Chest x ray showed ischemic (17%), congestive (69%), fibrotic and inflammatory (14%) changes.

Conclusion: Chronic lung lesion is common in sickle cell disease associated with rising white cell count, platelet count. All adult patients should have regular spirometry done to ensure early detection.

Keywords: Sickle cell disease, Tricuspid, Regurgitant, Jet velocity, Spirometry.

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Sickle cell disease is the most common inherited genetic disorder in the West African sub region. It has a stable gene frequency of 2.4% homozygote (Hb SS) in southwest Nigeria (1). The point mutation in position 6 of the beta globin gene results in the replacement of hydrophilic glutamic acid by a hydrophobic valine. The consequence is hemoglobin SS with reduced solubility in deoxygenated state and a low affinity for oxygen. The hemoglobin in low oxygen tension in the capillaries and venules releases its oxygen content and polymerizes. The crystals deform the skeletal proteins and the membrane phospholipids such that the cell becomes more rigid and the membrane becomes more adherent to the endothelium and other blood cellular elements (2). The result is blockage of the microvasculature, hemolysis, release of inflammatory cytokines and mitogens. With hemolysis, there is a release of hemoglobin and arginase. The hemoglobin mops up the constitutive nitric acid which reduces vasoconstriction, platelet activation, vascular fibrosis and vascular muscle proliferation while arginase mops up arginine which is a substrate for the production of nitric oxide (2-6).

Interstitial lung disease, which is characterized by vascular remodeling and interstitial fibrosis, is a frequent complication of sickle cell anemia (7). Circulating mesenchymal cells (fibroblasts), in a state of hypoxia during vaso-oclusive crises, express increased chemokine receptors (CXCR4). There is an extravasation of these activated fibroblasts in the lungs in response to the chemokine ligand (CXCL12) and consequently, there is a promotion of pulmonary fibrosis (7, 8). Various studies have shown that there is reduced pulmonary function in adult patients with sickle cell disease (5, 6). Suggested pathology were the interstitial abnormalities caused by repeated acute chest syndrome, airway hyperactivity, nocturnal oxyhemoglobin desaturation, pulmonary hypertension and thromboembolism (9-13). Chronic lung disease with generalized fibrosis and restrictive lung function defect is established in about the second decade of life and death in about the fourth decade (14-19). As study by Fawibe et al. in Nigeria showed that 18.9% of adult sickle cell anemia patients have chronic lung disease and this increases with age (20). The study by Klings et al, showed a prevalence of 90% (18). Chronic lung disease is therefore common in sickle cell anemia and respiratory failure is a common cause of sudden death in these patients. This study was to characterize this phenomenon in sickle cell adult patients with disease attending the clinic.

Methods

The study population was the patients with sickle cell disease in a steady state attending the adult hematology clinic of the hospital. Institutional ethical approval was obtained from the hospital research and ethics committee. Written consents were obtained with due explanations from the participants or their guardians if the age was less than 18 years. The inclusion criteria were hemoglobin SS in steady state. The patients with history of smoking, hepatitis, asthma, tuberculosis, renal or heart failure and those with chest deformity were excluded.

The full blood count and the red cell indices were done with the Sysmex hematology autoanalyser model KX-21N within 2 hours of sample collection. The fetal hemoglobin was assessed using the modified Betke's method. Chemical pathology tests were done manually using Randox kits. Oxygen saturation was determined with pulse oxymeter. The chest x-ray films were interpreted by the same consultant radiologist in the hospital.

The pulmonary function tests: They were done using the analog vitalograph 2150 spirometry in accordance with the American Thoracic Society standardization guidelines for acceptability and reproducibility criteria (21). The best two of three tests were recorded provided the difference was less than 0.2 liters. The percent predicted value for forced expiratory volume in first second (FEV1), forced vital capacity (FVC) and the peak expiratory flow rate in liters per minute were calculated on the basis of body mass index, age and sex with allowance for racial difference. The participants were given bronchodilator (salbutamol 200ug) and the percent changes in volume noted. The pulmonary function was considered normal if FEV1 and FVC predicted were at least 80% and FEV1/FVC ratio was at least 70%. Obstructive lesion was considered if FEV1/ FVC ratio was less than 70% and FEV1 was less than 80% while restrictive lesion was considered if FEV1/FVC ratio was at least 70% and FVC was reduced. Mixed lesion was considered if FEV1/FVC ratio was < 70% while FEV1 and FVC were < 80% (22). The transthoracic echocardiographies were done by the same cardiologist in the hospital using the Esaote Biomedica SIM 7000 CFM challenge in accordance with the guidelines of the American Society of Echocardiography.

Demographic and laboratory measures were presented as means ± standard deviations and medians. The association of data was determined by grouping them into normal and abnormal spirometry test and comparing the means or median using unpaired t-test for parametric data and Mann-Whitney test for nonparametric data as appropriate. The Spearman Rank or Pearson correlation tests for data with non-Gaussian and Gaussian distribution respectively were used as appropriate for assessing the relationships of the spirometry test with measured parameters. A contingency table of normal and abnormal chest x-ray findings with normal and abnormal spirometry was drawn to determine their predictability.

Results

The number of participants that gave consent was 64 but 8 were excluded on the account of other co-morbid conditions. Two participants did not meet the criteria for spirometry and one participant had the evidence of pulmonary edema on chest x-ray. The age range was 14-42 years with a mean age of 22±6 years and 60% of them were females. The mean body mass index was 17.84±1.78 kg

The mean percent forced expiration volume in the first second was 82.2%±16.5, in which percent forced vital capacity was 76.49%±16, mean peak flow rate was 340 l/minute±105. The mean ratio of percent forced expiratory volume to forced vital capacity was 85.6±8.4. In 21% of cases, there was a significant increase (> 12%) in the measured volumes after salbutamol. The mean oxygen saturation was 95.6±3.8. In patients with abnormal lung function, the mean oxygen saturation was reduced compared to those with normal lung functions (95.46±4.32 vs. 95.86±2.4) (p>0.05).

The prevalence of abnormal pulmonary function using simple spirometry was high (68%). The most frequent abnormality was restrictive lung lesion (53%). Other abnormalities were obstructive lesions (3.7%) and mixed lesions (11.3%) and the rest of the patients were normal.

The hematology and chemistry tests measured parameters were grouped into those with normal and abnormal spirometry. There were no significant differences between the groups with regard to hematocrit mean corpuscular hemoglobin concentration, fetal hemoglobin levels, lactate dehydrogenase, aspartate transferase and tricuspid regurgitant jet velocity (table 1). However, the means between the two groups regarding to white blood cell count (8.13 vs. 11.16 x 10^9/l), platelet count (291 vs. 467 x 10^9/l) and age (27.6 vs. 21years) had significant differences (p<0.05). The white cell counts and platelet counts had negative correlation with the percent forced vital capacity while age had a positive correlation.

Chest x-ray: The occurrence of abnormal chest x-ray was high (84%). The abnormalities were cardiomegaly (42%), fibrosis (2%), pulmonary infiltration (10%), plethora (6%), upper lobe blood diversion (10%) and peripheral vessel opacity (14%). All the patients with obstructive lung lesions had abnormal x-ray findings while 60% of restrictive and mixed lung lesions had abnormal x-ray findings. The contingency table was used to determine the predictability of chest x-ray findings and spirometry findings. The sensitivity was 37.5%, specificity was 88.1%, positive predictive value was 37%, negative predictive value was 88.1% and the likelihood ratio was 3.15. A normal chest x-ray finding is therefore likely to have a normal finding on spirometry.

Table 1. Analysis of difference in means of normal and abnormal spirometry test and the correlation with the forced vital capacity (no: 53, 17, 36)

	Total mean (53)	Mean of normal Spiro (17)	Mean of abnormal Spiro (36)	P.value of difference	Correlation coeficient	P.value
Hematocrit (%)	23.5±4.9	22.69±4.7	23.64±5.2	0.631	-0.2288	0.22
White Blood Count X 10^9/L	9.87±3.4	8.13±3.32	11.16±3.5	0.0319	-0.3385	0.0673
Platelet X 10^9/L	401±193	291±148	467±141	0.003	- 0.5130	0.0037
Mean Cell Hemoglobin Conc. g/L	33.4±1.03	33.68±0.87	33.345±0.94	0.1935	+ 0.09758	0.61
Hemoglobin F %	6.61±4.8	6.18±3.6	4.18±3	0.5722	+ 0.096	0.64
Age in years	22±6	27.6±6	21±5	0.0003	+ 0.4744	0.0003
Lactate Dehydrogenase	271±127	244±97	301±135	0.144	- 0.0162	0.9071
Aspartrate Transferase	32.2±23.8	34.2±23.5	35.11±27.98	0.9149	+0.2177	0.1174
O_2 Saturation	95.62±3.8	95.87±2.4	95.45±4.3	0.88	0.055	0.73
Tricuspid Regurgitant jet Velocity m/sec	1±0.5	1.133±0.54	0.92±0.4	0.1029	- 0.2156	0.1286

Discussion

The high prevalence of abnormal pulmonary function (68%) in the study was not as high as 90% reported by Kling ES et al. This is because this study did not include carbon monoxide diffusion capacity tests which accounted for about 13% of abnormalities in their study (18). However, aprevalence of 68% in these young participants and from a commercial center of the country where health facilities are available suggestive of the need to have regular pulmonary function test done in the adult sickle cell clinic. In Leong et al.'s study, 73% of patients with sickle cell disease showed

signs of pulmonary hyperreactivity but in this study, 21% of those with abnormal pulmonary function had adequate response to bronchodilator (23). The difference in prevalence may be explained by the difference in age and the inclusion criteria as obstructive lesions are more prevalent in children. The appropriate use of bronchodilators may be beneficial in 21% of patients with reduced pulmonary function in adults. The mean oxygen saturation was 95.62, this was higher than 92.5 reported by Homi J et al (24). There was no significant difference in the oxygen saturation of participants with lung lesion and those without lung lesion (p=0.88). The low affinity for oxygen associated with hemoglobin SS may contribute to this observation. A larger sample size will be necessary to make conclusions.

In 5% of sickle cell disease patients, there is lung hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAID) (25). It is therefore important to observe the patients on NSAID closely during vaso-oclusive crises and to warn such patients on the possible worsening of symptoms after NSAID administration since sickle cell disease patients are at increased risk of chronic lung lesion.

Restrictive lung lesion is common (53%) in this study. Most studies have demonstrated that restrictive lung lesion is common in adult patients as opposed to obstructive lesions in children (17-20). This will further worsen the intolerance to exercise due to anemia. Abnormal x-ray finding was observed in 84% of participants against the 68% with spirometry. The difference might be due to noninclusion of diffusion test which might increase the prevalence of abnormal function test to 90% (23).

An abnormal chest x ray finding has a 37% chance of having an abnormal pulmonary function while a normal x-ray has 88% chance of having a normal pulmonary function. The predictive values are likely to improve if carbon monoxide diffusion capacity test was included

The pathogenesis of chronic lung lesion in sickle cell disease may be inferred from the chest x-ray findings. Peripheral pulmonary vessels opacity suggests ischemic lesion (17%), cardiomegaly, plethora and upper lobe blood diversion would suggest congestive lesion (69%), fibrosis and infiltration may suggest inflammatory lesion (14%).

Congestion seems to contribute more. Contributory factors may be sequestration crises in the lungs, hyperdynamic circulation in sickle cell disease and ventricular failure. Therefore the drugs that will reduce the venous return to the heart may be helpful in chronic lung lesion of sickle cell disease. The factors that promote ischemia are increased blood viscosity due to sickling, vasoconstriction due to reduced nitric oxide and vascular media and intima proliferation in reaction to released mitogens and reduced nitric oxide. The possible therapeutic approaches are: inhalation of nitric oxide with oxygen by nebuliser, admistration of hydroxyurea, regular intake of arginine supplement and chest exercise. The selective use of these agents requires further studies. The factors that promote fibrosis are inflammatory reaction to sickling, increased tendency to pulmonary infections a status post auto-splenectomy, hyperreactivity of the lung, activation of fibroblasts and increase in white cell and platelet counts.

The changes in vital capacity had no significant correlation with hematocrit, lactate dehydrogenase and fetal hemoglobin as in other studies (17-20). Therefore, hemolysis, being a constant event in sickle cell anemia and also a function of the level of hemoglobin F, probably has a threshold effect on lung function and in other chronic organ damage.

In this study, the vital capacity increased significantly with age though lung lesions are expected to increase with age. An explanation is that most of the participants are still growing. The increase in vital capacity with age probably outweighs the effect of the disease.

In conclusion, chronic lung lesion is very common in adult sickle cell patients and restrictive lesions predominate. Adult patients are expected to have regular pulmonary function test done with trial of bronchodilator. Regular chest exercise, use of hydroxyurea and antibiotics to reduce white cell count, platelet count and lung infection may be of benefit. A limitation to this study is the small sample size. The study of carbon monoxide diffusion capacity would have increased the sensitivity of detecting more pulmonary function abnormalities.

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Conflict of Interest: None declared

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