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Sickle Cell Chronic Lung Disease among Young Adult Nigerians

La Cellule de Faucille la Maladie de Poumon Chronique parmi de Jeunes Nigérians Adultes

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ABSTRACT

BACKGROUND: **Sickle cell chronic lung disease (SCLD) is often underappreciated by health care providers because its exact prevalence and methods of diagnosis have not been well studied.**

OBJECTIVE: **To describe the pattern of SCLD among young adult Nigerians with sickle cell anaemia (SCA).**

METHODS: **Ninety (43 males and 47 females) patients with SCA who were selected by balloting and 90 (54 males and 36 females) healthy subjects with normal adult haemoglobin were studied. Their ventilatory function test (spirometry and peak expiratory flow rates), radiological and electocardiographic parameters were obtained and analyzed for SCLD.**

RESULTS: **Seventeen (18.9%) of the patients had SCLD. Majority (94.1%) of them were in stage1 disease, 5.9% in stage two, and none in the more advanced stages3 and 4. The number of patients with SCLD increased with increasing age. SCLD was associated with more than five previous hospital admissions (82.4%, OR=10.02, CI=4.51–22.22) and presence of symptoms suggesting previous acute chest syndrome (dyspnoea in 58.8%, OR=33.33, CI=7.39-150.30; chest pain in 94.1%, OR=81.33, CI= 9.83-672.85; cough in 47.1%, OR=64.00, CI=7.15-572.60).**

CONCLUSION: **SCLD may not be a rare event in Nigeria. Therefore efforts should be made to diagnose it in the early asymptomatic stage so as to offer effective intervention therapy to halt progression to the more disabling advanced stages. WAJM 2010; 29(1): 30–33.**

Keywords: **Sickle cell anaemia; chronic lung disease; adult; Nigerians.**

RÉSUMÉ

CONTEXTE : *la maladie de poumon chronique de cellule de Faucille (SCLD) est souvent underappreciated par les pourvoyeurs de santé publique parce que sa prédominance exacte et méthodes pour la diagnose n'ont pas été bien étudiés.*

OBJECTIF: *décrire le dessin de SCLD parmi de jeunes Nigérians adultes avec l'anémie de cellule de faucille (SCA).*

MÉTHODES : *Quatre-vingt-dix (43 mâles et 47 femelles) les patients avec SCA qui ont été choisis en votant au scrutin et 90 (54 mâles et 36 femelles) les sujets en bonne santé avec l'hémoglobine adulte normale ont été étudiés. Leur épreuve de fonction de ventilatory (spirometry et pic expiratory les débits), les paramètres radiologiques et electocardiographic ont été obtenus et analysés pour SCLD.*

RÉSULTATS : *Dix-sept (18.9 %) des patients avait SCLD. La majorité (94.1 %) d'entre eux était dans la maladie stage1, 5.9 % dans le stade deux et personne dans stages3 plus avancé et 4. Le nombre de patients avec SCLD a augmenté avec l'âge augmentant. SCLD a été associé à plus de cinq admissions d'hôpital précédentes (82.4 %, OR=10.02, CI=4.51–22.22) et présence de symptômes suggérant le syndrome de caisse aigu précédent (dyspnoea à 58.8 %, OR=33.33, CI=7.39-150.30; la douleur de caisse à 94.1 %, OR=81.33, CI = 9.83-672.85; la toux à 47.1 %, OR=64.00, CI=7.15-572.60).*

CONCLUSION : *SCLD peut ne pas être un événement rare au Nigeria. Donc les efforts devraient être faits pour diagnostiquer il dans le premier stade asymptomatic afin d'offrir la thérapie d'intervention efficace pour arrêter la progression à plus d'invalidité a avancé des stades. WAJM 2010; 29 (1) : 30–33.*

Mots clé : *anémie de cellule de Faucille; maladie de poumon chronique; adulte; Nigérians.*

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Abbreviations: ACS, Acute Chest Syndrome; **ATS,** American Thoracis Society; **BTAS, FVC,** Forced Vital Capacity; **PEFR,** Peak Expiratory Flow Rate; **SCA,** Sickle Cell Anaemia; **SCLD,** Sickle Cell Chronic Lung Disease.

INTRODUCTION

Lung involvement which accounts for a mortality rate of more than 20% in Sickle Cell Anaemia (SCA) patients constitutes a paramount determinant of their survival.[1–3] Clinical pulmonary involvement in them commonly takes two forms; the acute chest syndrome (ACS) and sickle cell chronic lung disease (SCLD).[4] The SCLD first described by Yater and Hansmann[5] in 1936 is often underappreciated by health care providers. This is because its exact prevalence and methods of diagnosis have not been well established owing to lack of detailed epidemiological studies. As far back as 1958, Sproule *et.al.*[6] documented chronic lung disease in asymptomatic patients with sickle cell disease. Young *et al*[7] also documented similar lung disease characterized by restrictive ventilatory defect as well as perfusion and diffusion defects in their patients during symptom-free intervals.

SCLD is now defined by radiological and clinical features of ventilatory dysfunction (restrictive or obstructive) and pulmonary hyper-tension.[4] The pulmonary hypertension which is most frequent in older children and adults was initially thought to be mainly due to recurrent ACS, but emerging facts support chronic haemolysis as the major risk factor for its occurrence. [2,3,8] Although the early stages of SCLD are usually asymptomatic, it may later be characterized by progressive disabling dysnoea, exercise limitation, hypoxemia and chest pain of increasing severity. The chest X-ray (CXR) shows diffuse interstitial markings and pulmonary function tests reveal decreased lung volumes and a restrictive functional pattern without significant airway obstruction in the advanced stage.

A staging system (stages 1–4 of increasing severity) was proposed by Powars *et. al.*[9] for SCLD based on clinical, physiological and radiological criteria. This work was designed to study the pattern of SCLD in the studied population using some of the criteria proposed by Powars *et al.*[9]

SUBJECTS, MATERIALS, AND METHODS

Ninety (43 males and 47 females) subjects with homozygous sickle cell disease (SS) and ninety (54 males and 36 females) normal subjects with normal adult hemoglobin (AA) were studied. The study subjects were consenting patients from the adult sickle cell clinic of University of Ilorin teaching hospital (UITH) who were selected by balloting for yes or no. Only those that selected yes were included in the study. The controls were healthy consenting age- and sex- matched medical students and hospital health workers. All the patients were in a clinically stable state for at least six weeks at the time of the study. They were all life-long non-smokers with no clinical or radiological evidence of pulmonary tuberculosis or asthma. The controls were also life-long non-smokers with no clinical evidence of cardio-pulmonary disease and normal chest radiographs.

The diagnosis of sickle cell anaemia was based on clinical and haematological findings of life-long sickling disorder and haemolytic anaemia as well as haemoglobin (Hb) electrophoresis (using cellulose acetate strips) on the venous blood sample collected from the patients as described by International committee for standardization in haematology.[10] The controls were normal subjects with Hb AA (electrophoresis carried out as for the SCA patients).

The ethical clearance for the study was obtained from ethical committee of UITH. Also informed consent was obtained from all the subjects.

Information on demography, medical history and physical findings was obtained from the subjects using self-designed questionnaires.

Measurements

The height (centimeters) was measured without shoes and weight (kilograms) was measured in light clothing.

The forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured in liters at BTPS with computerized spirometer (Spirolite®303 by medical system international corp.) and the forced expiratory ratio (FEV %) was calculated from the obtained values. Peak expiratory flow rate (PEFR) in liters/minute was measured with a Wright's peak flow meter (Airmed, England) at ATPS. The techniques for the test were explained and demonstrated to subjects. All the ventilatory tests were done in the sitting position. The reproducibility of the ventilatory testing was determined using the American Thoracic Society (ATS) [11] criteria (largest FVC within 0.2L of next one and largest FEV_1 within 0.2L of next one). The best of three trials was recorded.

Chest X-ray was done in all the subjects (cases and controls) while electrocardiographs (ECG) were done in all the patients and one third of the controls (selected by balloting for yes or no). The result of the ECG was interpreted by a consultant Cardiologist from the cardiology unit of medicine department while that of the CXR was interpreted by a Consultant radiologist from radiology department of our hospital. Venous blood was obtained for Hb electrophoresis from all the subjects.

Statistical Analysis

Statistical analysis was performed using version 13.0 of the SPSS programme for windows. The mean ± SD, range and prevalence rates were calculated as appropriate. The odds ratio was also calculated for the prevalence rates of previous hospital admissions and symptoms suggesting acute chest syndrome in those with SCLD.

RESULTS

The ages of the subjects ranged from 18-32 years with a mean of 22.5 ± 2.9 years for the cases and 18-30years with a mean of 23.3± 2.5 years for the controls. The male: female ratio in the cases was 1:1.1 and 1.5:1 in the controls.

Using the staging system of SCLD proposed by Powars *et al.*[9], 117(8.9%) had SCLD based on pulmonary function test (PFT), CXR and ECG patterns.

The general characteristics of the patients with SCLD are summarized in Table 1. Sixteen (94.1%) of them were in the Stage 1 category, 1(5.9%) in Stage 2 and none in Stage 3 or 4. None of the controls had criteria diagnostic of SCLD. Seven of those with stage1 disease were males while the rest were females. The only subject with Stage 2 disease was a

Table 1: Distribution of Patients with Sickle Cell Chronic according to Sex, Ventilatory Defect and Mean Age.

Variable	Stage 1	Stage 2
Sex [Number (%)]		
Male	7(41.2)	1(5.9)
Female	9(52.9)	0(0)
Total	16(94.1)	1(5.9)
Ventilatory Defect [Number (%)]		
Restrictive	13(76.5)	1(5.9)
Obstructive	3(17.6)	0(0)
Total	16(94.1)	1(5.9)
Mean ± SD Age (years)		
Male	24.6 ± 1.8	25*
Female	23.4 ±1.3	**

Table 2: Relationship between Prevalence Rates of Previous Hospitalisation and Symptoms Versus Presence or Absence of Sickle Cell Chronic Lung Disease

	Prevalence Rates (%)			
Variable	SCLD	NSCLD	OR	CI
Hospitality <5	17.6	91.8	0.02	0.00–0.09
Admissions >5	82.4	8.2	10.02	4.51–22.22
Dyspnoea	58.8	4.1	33.33	7.39–150.30
Chest pain	94.1	16.4	81.33	9.83–672.85
Cough	47.1	1.4	64.00	7.15–572.60
Bone pain	94.1	93.2	1.18	0.13–10.78

SCLD, Subjects with Sickle cell chronic lung disease; NSCLD, Subjects without Sickle cell chronic lung disease; OR, Odd ratio; CI, 95% confidence interval.

male. Fourteen (82.4%) subjects (13 in Stage 1 and one in Stage 2) with SCLD had lung function results suggestive of restrictive ventilatory defect while the remaining 3 (17.6%) with obstructive defect were in Stage 1. The mean age in those with Stage1 disease was 24.6 ± 1.8 years for males and 23.4±1.3years for the females. The only patient (male) in Stage 2 disease was 25 years old.

Nine (52.9%) of those with SCLD were below the age of 25years. The number of those with SCLD increased with increasing age from 3(17.6%) in the 15-19 year group through 6(35.3%) in the 20-24 year group to 8(47.1%) in the 25-29 year group.

Table 2 shows that SCLD, when compared with NSCLD, was strongly associated with number of previous hospital admissions (82.4%, OR=10.02, CI=4.51-22.22) and presence of symptoms suggesting previous acute chest syndrome (dyspnoea in 58.8%, OR=33.33, CI=7.39-150.30; chest pain in 94.1%, OR=81.33, CI= 9.83-672.85; cough in 47.1%, OR=64.00, CI=7.15-572.60).The presence of previous bone pains (94.1%, OR=1.18, CI=0.13-10.78) was weakly associated with SCLD.

DISCUSSION

The staging system adopted for SCLD in this study was that by Powars et al[9]: it revealed a prevalence rate of 18.9%, with all of them in Stages 1 or 2. Although this study did not measure blood gases and pulmonary artery pressure like they did, their staging system can still be adopted since it is unlikely for stable patients with lung function, CXR and ECG results that fell within Stages 1 and 2 to have had abnormal blood gases and pulmonary hypertension. Previous studies have revealed that abnormal blood gases and clinically significant pulmonary hypertension were seen only in SCA patients with Stage 4 disease.[9,12] However, emerging facts suggest that pulmonary hypertension is a common complication occurring in ≥30-36% of SCA adults.[2,8,13] Further work to document prevalence of pulmonary hypertension is clearly indicated but this is not the aim of this work.

Despite the fact that the exact prevalence and methods of diagnosis of SCLD have not been established owing to lack of detailed epidemiological studies, the 18.9% prevalence obtained in this study is very high compared to that of about 4% reported earlier.[9,14] This high rate may be because ours was a cross-sectional study which reported findings among selected sickle cell subjects. The earlier longitudinal studies reported findings among all the sickle cell subjects on follow up at their sickle cell centres over more than 20 years. Furthermore, these previous studies were done in centres where medical care is better than ours.

All the subjects with SCLD in this study were in the early asymptomatic Stages 1and 2, .This finding is similar to that of Young *et al.*[7] in which all the nine subjects they studied were in the early asymptomatic Stages 1 and 2. The absence of stages 3 and 4 disease in this study may be due to relatively younger ages of the subjects. The mean age at diagnosis of SCLD in this study was lower than that previously reported.[9] In that report, the only patient in stage 4 disease was 33.1 years old whereas none of our patients was up to 30 years old.

The number of those with SCLD was also observed to increase with increasing age. This is in keeping with the fact that SCLD is a long-term complication of SCD. The finding suggests that many more cases of SCLD will be diagnosed since improvement in standards of living is expected to lead to increase survival among our SCD patients.

Restrictive ventilatory defect was seen in 82.4% of our patients with SCLD. This figure is similar to the 90% observed by Klings et al[15] in their patients. The slight difference may be because they

determined the total lung capacity in addition to spirometry. The ATS guidelines[16] recommend the use of total lung capacity as the best diagnostic test for the presence of restrictive disease. However this could not be measured in our patients owing to lack of facility. The few patients with obstructive disease were in Stage 1 disease. This is in keeping with observation by Koumbourlis *et al.*[17] that SCLD may sometimes manifest as obstructive lung dysfunction initially but later leads to the development of restrictive lung disease. However, we need to follow-up the lung function in these patients to find out if they will develop restrictive disease with time.

There was a significant relationship between SCLD and the number of previous hospitalizations. This might be due to the fact that those with more admissions had more severe disease with higher risk of end organ damage. We also observed a significant relationship between SCLD and previous symptoms suggesting acute chest syndrome (dyspnoea, chest pain and cough). Studies by Santoli *et al.*[18] also documented significant relationship between abnormality of lung functions and previous ACS. Pianosi *et al.*[19] did not notice any significant relationship between abnormality of lung function and clustering of ACS. This may be because their subjects were much younger with fewer episodes of ACS. No significant relationship was observed between SCLD and previous bone pain when compared to those without SCLD. This may be because it is the commonest form of crises in both groups, occurring in almost all of them.

There are at least two limitations to the interpretation of the results of this study. The small number of subjects involved might have inflated the prevalence rates reported in this study. Also we were unable to use all the criteria proposed by earlier workers owing to lack of appropriate facilities in our centre as at the time of the study.

In conclusion, in spite of these limitations, the prevalence rate of SCLD from this study suggests that it may not be a rare event among patients with SCA in Nigeria. With improved standards of living and increased survival many more cases of SCLD will be diagnosed since the prevalence increases with increasing age. The significant relationship between SCLD and the number of previous hospitalization for crises as well as previous symptoms suggestive of ACS indicates that development of SCLD may reflect severity of the underlining SCA. Routine pulmonary function test is therefore recommended for all patients, especially those with severe disease, so as to diagnose SCLD in the early asymptomatic stage, because this is the only hope for effective intervention therapy.

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