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ORIGINAL ARTICLE

Frequency of Hepatomegaly and Splenomegaly in Nigerian Patients with Sickle Cell Disease

Fréquence des hépatomégalie et splénomégalie nigériane patients avec Drépanocytose

J. A. Olaniyi*, U. M. Abjah

ABSTRACT

BACKGROUND: **Hepatobiliary and splenic complications (amongst others) are common in sickle cell disease (SCD) as a consequence of the progressive injury resulting from repeated sickling of HbS red blood cells.**

OBJECTIVE: **To determine the degree and the frequency of persistent hepatomegaly and splenomegaly in relation to determinants of clinical severity in patients with SCD.**

METHODS: **Two hundred and twenty SCD patients in clinical steady state were assessed for the presence and the size of palpably enlarged spleen and liver. Patients with hepatomegaly or splenomegaly were re-assessed after three months. Average size was recorded as well as the electrophoresis pattern, age at asessment, sex and the haematocrit. These were compiled over one year**

RESULTS: **The mean age of the SCD patients was 24.7(8.7) years. HbS and female subjects predominated, constituting 89% and 57% respectively. Females had statistically significantly higher mean age of years than males, ($p< 0.001$). Splenomegaly was present in 46(21%) of SCD patients, of which 39(84.8%) were HbSS, with a mean splenic size of 8.7(7) cm. Out of the 220 SCD patients, hepatomegaly was present in 59%, with a mean size of 7.6(6.5) cm. However, higher frequency and a significantly bigger size of hepatomegaly were found in patients with HbS than in those with HbSC. The mean age of 27.2 (10.9) years and the mean of PCV of 24.1(4.9) in the 82 (37%) patients without hepatomegaly and splenomegaly were significantly higher ($p =0.001$) than the general population of SCD patients studied.**

CONCLUSION: **Hepatomegaly of varying sizes occurs commonly in patients with HbS and probably connotes a severe clinical course. The aversions that there is predominance of HbS, survival advantage of females and the fact that HbSC fair better than HbS remain true. WAJM 2007; 26(4): 274–277.**

Keywords: ***Anaemia, Sickle Cell Disease, Hepatomegaly, Splenomegaly, Haemoglobin phenotype.***

RESUME

CONTEXTE: *hépatobiliaires et complications spléniques (entre autres) sont courantes dans la drépanocytose (SCD) en conséquence de la progressive résultant de blessures répétées sickling HbS de globules rouges.*

OBJECTIF: *Déterminer le degré et la fréquence d'une hépatomégalie et une splénomégalie persistante par rapport aux déterminants de la sévérité clinique chez les patients ayant une SCD.*

MÉTHODES: *Deux cent vingt patients dans les cliniques SCD à l'état d'équilibre ont été évalués pour la présence et la taille de sensiblement élargie, la rate et du foie. Les patients ayant une hépatomégalie ou splénomégalie ont été réévalués au bout de trois mois. Taille moyenne a été enregistrée ainsi que le schéma d'électrophorèse, à l'âge de asessment, de sexe et de l'hématocrite. Celles-ci ont été compilés sur un an.*

RÉSULTATS: *L'âge moyen des patients était de SCD 24,7 (8,7) ans. HbS et sujets femelles prédominent, constituant 89% et 57% respectivement. Les femelles ont statistiquement significativement plus élevés âge moyen d'années que les hommes ($p <0,001$). Splénomégalie était présente dans 46 (21%) des SCD patients, dont 39 (84,8%) ont été HbSS, avec une taille moyenne splénique de 8,7 cm (7). Sur les 220 patients SCD, une hépatomégalie était présente dans 59%, avec une taille moyenne de 7,6 cm (6,5). Toutefois, une fréquence plus élevée et une plus grande taille de manière significative une hépatomégalie ont été trouvés chez des patients atteints d'HbS que dans ceux avec HbSC. La moyenne d'âge de 27,2 (10,9) ans, et la moyenne de PCV de 24,1 (4,9) dans le 82 (37%) patients sans hépatomégalie et une splénomégalie ont été significativement plus élevé ($p = 0,001$) que la population générale de patients étudiés SCD.*

CONCLUSION: *Hépatomégalie de différentes tailles se produit fréquemment chez les patients atteints d'HbS et, probablement, une forte connotation clinique. Les aversions qu'il ya prédominance de l'HbS, à la survie des femelles et profiter du fait que HbSC juste HbS mieux que rester fidèle.* ***WAJM 2007; 26(4): 274–277.***

Mots clés: *anémie, la Drépanocytose, hépatomégalie, splénomégalie, Hémoglobine phénotype.*

Department of Haematology, University College Hospital, PMB 5116, Ibadan; Nigeria. Email : johnniyi2001@yahoo.com. Tel: 2410088-2645or234-802-345-1509. †Department of Haematology, University of Maiduguri, Nigeria. Tel: 234-803 327-9811.
Corresponding Author. Dr. J. A. Olaniyi

Abbreviations: HbSS, Haemoglobin SS; SCD, Sickle cell disease; AbSC, SCA, Sickle cell anaemia.

INTRODUCTION

Sickle Cell Disease (SCD) refers to a group of haemoglobin (Hb) variants characterized by sickling syndrome of which HbS {Sickle Cell Anaemia (SCA)} is the most prevalent[1], followed by HbSC. Others in the group include HbS-D Los Angeles, HbO-Arab and Hb S-thalassaemia. Sickle cell disease is one of the commonest genetic disorders worldwide whose genetic basis was demonstrated in 1949.[1,2] SCA affects a significant number of people in Nigeria with generally severe clinical course[3,4] because of low HbF level (mean of 5-9%) linked to homogemously prevalemt haplotype #19 in Nigeria SCD patients.[5,6] Clinical presentations and complications in SCD greatly vary. This wide spectrum of presentation which ranges from the very mild to the very severe clinical course is governed by varying genetic determinants[7,8] which include co-existence with alpha and beta thalassemia.[9] Fetal haemoglobin,[10] beta haplotype associated with beta S chromosome.[11]

Whereas autosplenectomy (splenic fibrosis/afunctional spleen) occurs by the age of eight years in most SCD patients; those with factors conferring good clinical course retain their individual functional spleen. On the other hand those with bad disease suffer higher rate of repeated sickling and therefore numerous and more severe organ damage of which hepato-pathy with persistent hepatomegaly is one.

Prompted by the strong link between persistent hepatomegaly and clinical severity in sickle Cell Disease (SCD), this study therefore examined the degree and the frequency of persistent hepatomegaly/splenomegaly and the effect of sex, haematocrit, haemoglobin phenotype and age in SCD through clinical assessment.

PATIENTS AND METHODS.

Sickle cell disease patients attending sickle cell clinic were recruited into this study between March 2000 and February 2001 after an informed consent was obtained from individual patients.

Sickle cell status was confirmed by haemoglobin electrophoresis. Patients in discomfort or in any form of crisis were exempted. Haematocrit done on that day was noted and clinical assessment was done using sizes of spleen and liver. The mid-axillary, sub coastal size of spleen and liver were measured using a tape rule when such organs were clinically palpable. The age, sex and haemoglobin phenotype determined through haemoglobin electrophoresis were equally recorded. The selected patients were seen and reviewed again after three months during which the hepatosplenomegaly were re-assessed again purposely to ascertain that the organs were persistently enlarge and also to determine the average size. These data were then compiled and subjected to statistical analysis.

The statistical package EPI INFO version 6.04 of July 1996 was used for data entry and for frequency distribution of all the entries. PGC Gold was used for further statistical analysis. The student t-test was used to assess for differences between continuous variables and Chi square was used for discrete data. A p value of 0.05 or less was considered significant.

RESULTS

Two hundred and twenty patients with SCD in steady clinical state who had come for routine medical follow up were consecutively recruited into the study. The age range was 12-60 years with a mean age of 24.7 (8.6) years. Males constituted 95(43.2%) while 125(56.8%) were females. HbSS phenotype constituted 193(87.7%) of which 103(53.5%) were females. Also, HbSC phenotype patients were 27(12.3%) out of which 22(81.5%) were females. Females had statistically significant higher age than males, 27.2(9.90 v 21.4(5.0) years, p =0.000.

The overall mean PCV was 22.3(5.2%) with a range of 10-36%. No statistically significant sexual difference was found in the means of PCV. However, the mean PCV of HbSC patients was statistically significant higher than that of patients with HbS (27.3 (5.0%) v 26 (4.9%), p <0.0001.

Of the 220 SCD patients, 46(20.9%) had palpably enlarged spleen below the coastal margins; 39(84.8%) were HbSS and 7(15.2%) were HbSC (Table 1). The overall mean splenic size was 8.7(7) cm with a range of 2cm–20cm. There was no statistically significant difference between the mean spleen size in males compared to females, (8.8 ± 5.4cm) v 8.5(5.4) cm, p = 0.974.

Enlarged liver was observed in 129(58.6%) of the SCD patients, (Table 2); of which 120 (95.2%)) were HbSS patients (mean size of 7.8(3.9) cm compared to

Table 1: Spleen Enlargement according to Haemoglobin Phenotype in Patients with Sickle Cell Disease

Spleen status	Haemoglobin phenotype (N %)		
	HbS	HbSC	Total
Enlarged	39(84.8)	7(15.2)	46(100)
Normal	154(88.5)	20(11.5)	174(100)
Total	**193(87.7)**	**27(12.3)**	**220(100)**

Table 2: Liver Enlargement according to Haemoglobin Phenotype in Patients with Sickle Cell Disease

Liver status	Haemoglobin phenotype, N(%)		
	HbSS	HbSC	Total
Enlarged	120(95.2)	9 (4.8)	129(100)
Normal	73(80.2)	18(19.8)	91(100)
Total	**193**	**27**	**220**

Table 3: Relationship between Hepatosplenomegaly and Haemoglobin Phenotype in SCD patients.

	Hepatosplenomegaly, N(%)		
Hb Phenotype	**Present**	**Absent**	**Total**
HbSS	67(34.7)	126(65.3)	193
HbSC	15(55.6)	12(44.4)	27
Total	**82(37.3)**	**138(62.7)**	**220(100)**

9(4.8%) in HbSC 4.7(1.9) cm. The overall mean liver size was 7.6(6.5) cm (range 2cm-18cm). Although more females, 71(55.0%), compared to males, 58(45%), had enlarged liver, statistically significant difference was not observed (p = 0.645). The mean liver size in HbS patients of 7.8(3.9) cm was statistically significantly greater than that of HbSC patients with a mean liver size of 4.7(1.9) cm, p = 0.018.

Eighty two (37.3%) SCD patients had no hepatomegaly and splenomegaly of which 31(37.8%) and 51 (62.2%) were males and females respectively. However, no statistically significant difference was found when the males with hepato-splenomegaly were compared with those without. Out of the 82, 67(81.7%) were HbS and 15 (18.3%) were HbSC, see Table 3. The overall mean age of these 82 patients was a 27.2(10.9) years which is significantly higher than the overall mean age of the 220 SCD patients and also their mean PCV of 24.1(4.9) is higher than the overall mean PCV of 22.3±5.2%. The mean age of the females, within the group; was higher and statistically significant (p = 0.001) than males. The PCV of males compared to that of females did not show any significant difference (p=0.225). The mean age and the mean PCV of HbSC, also within the group; were found to be higher and statistically significant (p= 0.000 in both cases) than that of HbS patients.

DISCUSSION

Sickle Cell Disease patients suffer highly variable life long problem of chronic haemolytic anaemia and insidious vaso-occlusive crises resulting in progressive organ damage.[12] Hepato-biliary and splenic complications (amongst others) are common in SCD as a consequence of this progressive injury resulting from repeated sickling. Hepatobiliary complications include cholelithiasis, choledocholithiasis and acute hepatic failure. Liver biopsy in earlier studies confirmed sinusoidal dilatation, Kupfer cell hyperplasia and erythrophagocytosis.[13,14] Persistent hepatomegaly has been found to be an important severity index in sickle cell anaemia.[14,15]

The results of this study brought out certain established facts about sickle cell disease. First, HbS predominates (constituting about 87%), a finding that agrees with previous studies.[15,16,17] Secondly, females constituted a higher percentage (57%) and also have a statistically significant higher age than the males. This is in consonance with the postulated survival advantage confirmed by X chromosome,[17] survival advantage in females[18] and age and sex effects on HbF.[18,19] Thirdly, earlier works had documented mean haemoglobin of 7.6(1.3) g/dl for Hb S and mean Hb of 12.5 ±1.8g/dl for HbSC patients which correlates with the mean PCV of 22% (haemoglobin of 7.4) for all sickle cell disease patients in this present study and also a mean PCV of 27% for HbSC patients agrees with the previous works.[15,16,17]

Palpable spleen is expected to be an uncommon finding in sickle cell disease patients because of autosplenectomy that occurs early in life; however, in this present study about 21% of sickle cell disease patients had palpably enlarged spleen below the coastal margin. However, earlier workers had demonstrated that impalpable splenic tissue was visible on ultrasound in over 50% of subjects with HbS.[16,15] The spleen becomes fibrotic early in life at about the age of eight years as part of global progressive vaso-occlusive process culminating in infarction of tissues and organs.

However, a few patients endowed with favorable genetic and environmental factors conferring good clinical course happen to retain their functional spleen.[11,16,15] Such functional spleen can become enlarged following pathological processes involving the reticulo-endothelial cells as in chronic extra-vascular haemolysis and sequestration crisis which occur in sickle cell disease. Other causes of splenomegaly may not be far fetched in sickle cell disease.

Hepatomegaly was found in 59% of sickle cell disease patients. The presence and size of hepatomegaly appeared not to be influenced by the sex of the patient since no significant statistical difference was observed following comparison of mean size in males with that of females; however hepatomegaly appeared to be more frequent and bigger among HbS patients since statistically significant difference was observed when compared. This may signify a more intense chronic haemolytic process and occurrence of hepatitis of various aetiology in the HbS patients compared to HbSC and thereby explaining the higher haematocrit in HbSC patients.

This study equally showed that 82(37.3%) of our sickle cell disease patients happened not to have palpable hepatosplenomegaly. In this group females constituted 62% and HbS constituted 81.7%. Their mean age happened to be statistically significantly higher than that of the general population of SCD patients studied. This may suggest that sickle cell disease patients without persistent hepatosplenomegaly possibly have underlying genetic/environmental factors conferring a better clinical course. Again it may simply imply reduced reticuloendothelial destruction of red blood cells. Earlier workers had reported chronic hepatomegaly in SCD patients.[16,17,18] Some workers had singled out chronic hepatomegaly as a severity index in SCD.[19]

The variability in hepatomegaly and splenomegaly is in consonance with the diversity of various genetic/environmental factors governing the clinical course of SCD. One of the factors is the coexistence of alpha thalassaemia

which has been noted to reduce haemolytic rate in SCD.[20] Some of the SCD patients without hepatosplenomegaly may fall to these categories hence the need for further genetic study on this group of patients.

This study is considered relevant because simple physical examination revealing presence or absence of persistently palpable hepato-splenomegaly in SCD can be a guide to the clinical course of the disease and the expected range of steady state haematocrit in respect of age and sex.

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