East African Medical Journal Vol. 78 No. 7 July 2001
SURVIVAL ADVANTAGE IN FEMALE PATIENTS WITH SICKLE CELL ANAEMIA
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T.R. KOTILA and W. A. SHOKUNBI

ABSTRACT

Objective: **To evaluate the clinical and laboratory features of adult sickle cell anaemia patients in Nigeria.**
Design: **A cross-sectional study.**
Setting: **Haematology clinic of the University College Hospital, Ibadan, Nigeria.**
Subjects: **Sixty nine adult sickle cell anaemia patients randomly sampled.**
Results: **The mean steady state haematocrit, HbA_2 and HbF were 22%, 4.6% and 7% respectively. Twenty five per cent of the patients had never received blood transfusion and a similar proportion recorded an infrequent occurrence of painful crises.**
Conclusion: **An improved survival was observed with female patients showing an age related survival advantage over the males. Persistent splenomegaly was observed less frequently in the Nigerian sickle cell population despite the high frequency of alpha thalassaemia in the region. This was thought to be due to the lower levels of HbF in this population.**

INTRODUCTION

The sickle cell gene is present in high frequency in Nigeria with a heterozygous frequency of 24% in Southern Nigeria, a region where malaria is holoendemic and 30% in northern Nigeria, where malaria is hyperendemic(1). The clinical manifestations of the disease vary between patients in the same community and patients in different geographic regions(2,3). Many factors are known to be responsible for this variability in the clinical expression of sickle cell anaemia. A low socio-economic class, poor access to good medical care and poor compliance to adversely affect the overall picture of these patients and ultimately the morbidity status. Early diagnosis and simple prophylactic measures significantly reduce deaths associated with homozygous sickle cell disease(4).

Genetic factors are also known to affect the clinical severity of the disease. Sickle cell anaemia patients in Nigeria are believed to have the Benin beta-globin gene haplotype, which is characterised by the presence of a relatively low level of fetal haemoglobin(5). The low level of HbF is believed to be responsible for the poorer clinical state, unlike other haplotypes which are associated with a higher level of HbF(5,6). Concomitant inheritance of the alpha thalassaemia gene which occurs in 30 - 35% of people of West African origin, is another genetic factor that could affect the clinical expression of sickle cell gene.

A recent survey in Nigeria highlighted differences in clinical features of two contiguous ethnic groups of the same ancestry(3). In this study we relate the clinical features and laboratory parameters of adult sickle cell anaemia patients seen in the steady state at the follow up (routine) clinic of the University College Hospital (UCH), Ibadan, Nigeria to the gender of the patients.

MATERIALS AND METHODS

Every sixth HbS patient (at each clinic visit the patients were distributed randomly among six doctors) in the steady state seen consecutively at the adult sickle cell clinic of the UCH Ibadan Nigeria were recruited into the study. Steady state was defined as the absence of acute illness or of any chronic condition likely to influence haematology(7). The study was carried out over a period of six months. Patients who presented at the clinic with an acute illness or were transfused within the preceding three months were excluded from the study. Also excluded from the study were pregnant women.

The age and sex of the patients were noted. The patients were asked the frequency of bone pains per year. This was classified into three groups: those with 0-1 bone pain episode per year 2-3 episodes per year and greater than three episodes in a year. History of blood transfusion was similarly classified into those who had never been transfused, those who had only received one unit and those who have had more than one unit transfused. The information was confirmed from the case file.

A single observer did a physical examination of all the patients. The presence or absence of splenomegaly and/or hepatomegaly was noted but this was not confirmed by ultrasonography. Steady state haematocrit was determined by averaging the results of at least four haematocrit readings in the steady state recorded in the case file (all HbS patients that attend the adult Haematology clinic routinely have their haematocrit done every three months).

2.5ml of venous blood was collected into standard EDTA bottles (contained 3mg of the anhydrous salt). HbA_2 level was

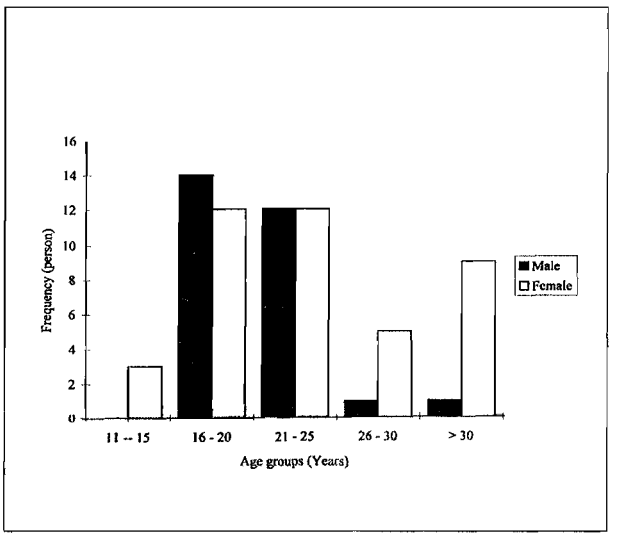
quantified by elution after electrophoresis on cellulose acetate paper while HbF was analysed by the alkaline denaturation method using an analogue spectrophotometer (Pye-Unicam SP6 -200).

RESULTS

The study population included 28 males and 41 females (male/female ratio 1:1.5). The age of the study population ranged between 12 and 43 years, with a mean age of 22 years. The mean age of the females was 24 years while that of the males was 21 years. Fourteen per cent of the patients were over 30 years. There were more females than males in the older age group (Figure 1).

Figure 1

Sex distribution according to age

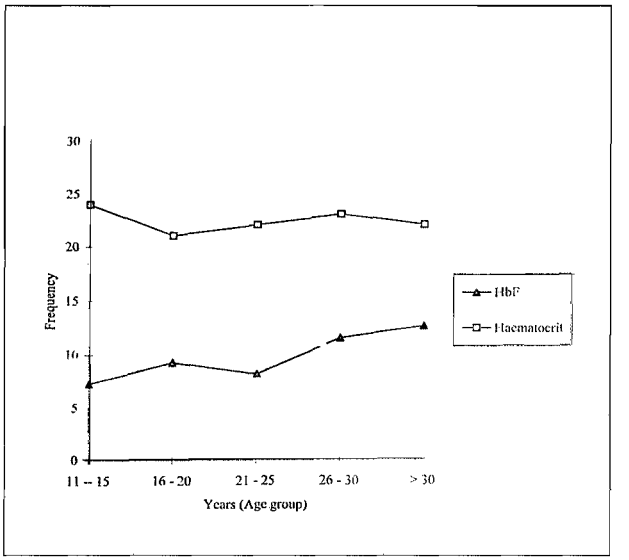


Haematologic parameters: The mean steady state haematocrits was 22% (16 - 29%). None of the subjects had a value ≥30% (Table). The mean HbF and HbA_2 were 7.0 ± 3.4% and 4.6 ± 1.3% respectively. Female patients had a mean HbF of 6.7% while males had a mean of 7.6%. The mean PCV of the sexes was 22%. The patients, gender did not affect the mean haematocrit, HbF or HbA_2 significantly. Though HbF rose with age, a corresponding rise in haematocrit was only observed in patients between ages 16-30 years. Figure 2 shows the relationship between the haematocrit HbF and the different age groups.

Acute painful crises and transfusion requirement: Twenty five per cent of the patients rarely had painful crises (bone pains) while half (50%) had less than three painful episodes per annum. Others had three or more painful episodes in a year. Nineteen (27%) of the patients had never received blood transfusion. Twenty per cent had received blood transfusion only once, while 53% had received blood transfusion more than once. The mean haematocrit and HbF for those who had not been transfused was 23% and 10.8% respectively, while the mean for those who had received at least one unit of blood was 22% and 7.4% respectively.

Figure 2

Relationship between haematocrit and HBF



Organ enlargement: Forty six per cent of the patients had no abdominal organ enlargement. Splenomegaly was observed in 16% of the patients. The splenic enlargement was between 2 cm - 16 cm below the costal margin. Forty-six per cent had hepatomegaly of 4 - 14 cm below the costal margin. Both organs were enlarged in 8% of the patients.

Complications: Symptomatic coagulation failure defined as bleeding in the presence of deranged coagulation profile (prolonged prothrombin time and activated partial thromboplastin time) was observed in three patients; two females and one male. Two of these patients had moderate hepatomegaly.

A healed or active leg ulcer was observed in six out of sixty nine (8%) of the patients (three males and three females). Severe avascular necrosis of the femoral head affecting the gait of the patients was observed in 8% of the patients. Only one of these patients could afford a partial hip replacement. Four of the patients (three males and one female) had at least one prior episode of a cerebrovascular accident (CVA).

DISCUSSION

There was an improvement in the survival of SCA patients compared with what was found in this environment about two decades ago. Fourteen per cent of the patients in this study were in the 4th or 5th decade. This may be an under-representation since it was observed that the older patients did not attend the follow up clinic but would rather present with an acute illness in the haematology day care unit. The improved survival may be attributed to better health care and increased awareness. Survival of Black children with sickle cell disease is known to have improved markedly since 1968(8) with a current median survival of approximately 40-50 years in the United States(9). Jamaican sickle cell anaemia patients are also known to

have a better survival than Nigerian patients with more patients in the age range of 40 - 73 years(7). There were more female patients than males and this was more apparent in the older age group (Figure 1). This may suggest that the female patients have a survival advantage over the males or that the female patients are more regular clinic attendees. This finding is not peculiar to this study only. Of the 181 Jamaican patients who were over 40 years studied by Morris *et al*(7), there were 109 females and 72 males. A study among the Saudis also showed a relative excess of females among patients from the Western province who had the Benin haplotype(2) as the patients described in this present study.

HbF appears to rise with age in our cohort of patients (Figure 2), which is in agreement with other cross sectional studies(10,11). This, however, has been attributed to the survival advantage which patients with high levels of HbF have over those with low levels of HbF. Reports on the influence of sex on HbF have been conflicting(10,12). This study which dealt with patients who are mostly below 40 years of age showed a none significant difference between the sexes. The study by Morris *et al*(7), showed a striking sex difference in the behaviour of HbF with age, values being steady in females but falling in males. HbF may therefore be a factor associated with the better survival observed in the female patients.

In as much as painful crisis and recurrent anaemia is a common mode of presentation in patients with sickle cell anaemia, it is impressive that twenty five per cent of the patients rarely had painful crisis while a similar proportion had never been transfused. The non-significant positive relationship between the frequency of bone pains and blood transfusion might be due to the "top-up transfusion" which was often an adjunct to therapy in patients with intractable bone pains. This association may disappear with the less frequent use of "top-up transfusion" in the management of intractable bone pains. Persistent splenomegaly is often attributed to high HbF level or homozygous alpha thalassaemia. Splenomegaly was observed in 16% of our patients which is comparable to a previous study(3) in which splenomegaly was observed in 26% of patients which included the paediatric age group. The Nigerian population has a lesser frequency of persistent splenomegaly compared to the Saudis who were found to have a prevalence of 30 - 53%(2). This might be due to the higher level of HbF found in the sickle cell disease patients of the Indian-Arab population.

The survival advantage noted in the females has not been shown in this study to be related to the level of HbF. The survival was also noted more in the older age. There is a need for a longitudinal study to confirm the rise in HbF with age and to establish if the survival advantage in females was due to rising HbF level.

ACKNOWLEDGEMENTS

To the Director of Clinical Services, Research and Training, University College Hospital, Ibadan for permission to publish this work.

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