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Haemoglobin F and clinical severity of sickle cell anaemia among Nigerian adults

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Summary
Haemoglobin F (HbF) has been a useful criterion in predicting the clinical severity of sickle cell disease (SCD). Thus different treatment modalities are geared towards raising its level. This study estimated HbF levels in sickle cell anaemia patients. HbF levels were then compared with clinical parameters such as the average number of bone pain crisis per year, transfusion requirement, enlargement of both the spleen and liver and the haematocrit level. The mean HbF value was 7.4 ± 3.6%. Males recorded a higher mean level than females 7.6 ± 3.9%, and 6.7 ±3.6% respectively, ($P > 0.05$). HbF of 7.4% was used to divide the patients into two broad groups. Patients with HbF of more than 7.4% were older compared to those with less than 7.4% ($P > 0.5$), the former group was also less transfusion dependent ($P > 0.05$) even though their haematocrit was not significantly different ($P > 0.05$) from those with HbF of < 7.4%. The patients with higher HbF levels are also more likely to retain their spleen longer than their counterpart with lower values. It appears that clinical severity has a relationship with HbF values even though most were not statistically significant. There is a need for larger studies to study this relationship more closely.

Keywords: *Clinical severity, sickle cell anaemia, HbF*

Résumé
L'hémoglobine F (HbF) a été un criteré utile dans la prédiction de la sévérité clinicale des maladies aurx hématies falciformes. Alors, les différentes moldalités de traitement sont dirigées á augmenter son nivean. Cette étude a estimé la quantité de HbF chez les patients sonffrant de l'amémie falciforme. Le taux de HbF a été comparé avec les paramétres chniques tels que le nombre moyen des crises du mal ddes os par an, la demande de transfusion, l'élargement á la fois de la rate et du faie et le taux d'haemotocrite. Le taux moyen de HbF était de 7,4±3.6%. Les hommes avaient un taux moyem plus élevé que les femmes 7.6 ±3.9% et 6.7 ±3.6% respectivement ($P>0.05$). 7,4% de taux de HbF a été utilise pour divider les patients en daux en daux grand groupes. Les malades ayant in taux supériur á 7,4% ($P > 0,5$), le dermier group ne dependant pas beanconp de la transfusion ($P > 0,05$) bien que leur haematocrite n'était pas trés différent ($P > 0,05$) de ceux avec HbF inférienre á 7,4%. Les patients ayant un taux élevé de HbF ont plus de chance de retemir leur ... Longtemps que leur partemaire avec un taux faible. It aparait que la sévérité clinique a une relation avec la quantité de HbF, bien que la plupart n'était pas statisticallement significative. Il en découle un grand besoin d'étude, pour pouwoir établir cette relation plus chairement.

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Introduction

The treatment for sickle cell disease (SCD) is largely supportive since treatment like bone marrow transplantation is a procedure for a selected few, and cure by gene therapy is a thing for the future. Other treatment modalities for SCD are known to work by increasing fetal haemoglobin (HbF) synthesis, the agents used in such treatment could be cytotoxic drugs, growth factors or agents inducing differentiation.

The level of HbF is known to vary in SCD patients from different localities and even among those within the same locality [1,2]. HbF has been used to predict the clinical severity of this disorder, the prediction of severity based on HbF is however not absolute since there is an interplay between HbF and other genetic factors. This might be responsible for the difficulty in determining characteristics which favour survival. Numerous factors known to influence the level of HbF include the age and sex of the patients and the number of active α- globin genes [3]. This study assessed the effect of HbF on the clinical features of the disease in our environment and possibly predicts severity of the disease and survival. This has the advantage of reducing patient disability, morbidity and in fact mortality. It will also reduce some of the physical, financial and emotional burdens experienced by the patients' caregivers and family.

Patients and methods

Fifty sickle cell anaemia patients in steady state were selected by the systematic sampling method from the adult haematology clinic of the University College Hospital, Ibadan, Nigeria. Information was collected using an interviewer-administered semi-structured questionnaire, information obtained were demographic details such as age and sex of the patients. Also, history of blood transfusion and average of number of crisis per year were obtained. In addition, a physical examination was done to determine enlargement of the liver and spleen. laboratory investigations done included the following:

1. Haematocrit was determined by computing the average results of four haematocrit readings obtained in the steady state.
2. HbF was determined by the alkaline denaturation method of Betke [4] using an analogue spectrophotometer (Pye Unicam SP-600).

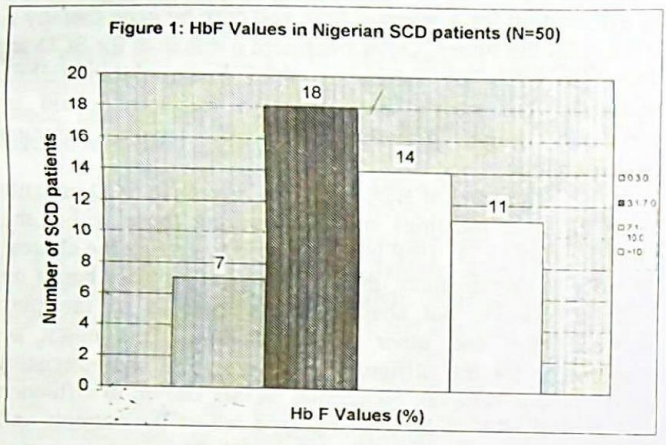
The mean HbF level of 7.4% was used as a denominator to classify the patients into two groups. Twenty-six and 24

patients had HbF value ≤7.4% and >7.4%, respectively. Blood transfusion history and number of bone pain crises per year were compared between the two groups.

Data were analysed manually, with EPI-INFO version 6 and with EPI-stat software packages. Due to the small sample size, the Fischers Exact Test was used to determine differences in findings between the two broad groups. P values of less than 0.05 were accepted as significant.

Results

The frequency distribution of the patients' HbF is shown in figure 1. Most (32 or 64%) patients had HbF values between 3.1% and 10.0%.



The mean HbF was 7.4 ± 3.6%. Males had a higher mean HbF value of 7.6 ± 3.9% while the females had a mean value of 6.7 ± 3.6%, the difference was not statistically significant (F =2.61, $P > 0.0$). The male/female ratio was 1:1 in patients with higher HbF levels, while those with HbF of < 7.4% had a ratio of 1:2 (Table 1). The patients studied included three families with siblings of both sexes, in two of the families the males had higher HbF levels, while in the third family the female had a higher HbF level.

Table 1: Comparison of demographic indices between patients with Hbf < 7.4% and those with Hbf > 7.4%

Demographic characteristics		HBF≤7.4% N = 26		HBF>7.4% N = 24	
Sex	Females	17	(68%)	12	(48%)
	Males	8	(32%)	13	(52%)
Age	>30yrs	2	(8%)	5	(20%)
	<30yrs	23	(92%)	20	(80%)

The clinical effect of HbF on the patients was determined by grouping the patients based on the mean HbF of 7.4%. Patients with higher HbF levels (>7.4%/) were less transfusion dependent ($P > 0.05$), 20% compared with the counterparts with lower values (12%). Also, they were found to have hepatomegaly less often than those with lower values (57.7% compared with 33.3%, $P > 0.05$) (Table 2).

Table 2: Comparison of severity among patients with HBF of greater and less than 7.4%

Clinical Severity	HBF< 7.4% (N=26)	HBF>7.4% (N=24)	Fischers Exact	P Value
*NHBT	3 (11.5%)	5 (20.8%)	4.16	0.305
#0-2BPC/Yr	8(30.8%)	3(12.5%)	1.48	0.224
Hepatomegaly	15(57.7%)	8(33.3%)	2.08	0.149
Splenomegaly	3(11.5%)	5(20.8%)	4.16	0.305
Mean PCV	21.6 ± 3.2	22.5 ±2.4	3.62	0.269

**NHBT =No history of blood transfusion.*
#BPC/yr = Bone pain crises per year.

Discussion

The mean HbF obtained is similar to that of previous indings in this environment [1,5] which also agree with the mean bF described for the Benin haplotype [6]. The frequency of HbF in this study showed most of the patients had HbF of 3-10%, this is in contrast to a previous study which showed majority of the patients as having HbF of less than 6%[5].

Other studies have shown higher levels of HbF in females and this has been attributed to the linkage between HbF production and the chromosome X locus [5,7]. Higher HbF levels was observed in males, this is not peculiar to this study [8], Chang *et al.* have also identified two families that are compatible with either autosomal or X linked factor controlling the HbF levels but the variation in F-cell numbers were not linked to markers on the X chromosome [9]. Another plausible explanation for the reversal in the mean HbF level between the two sexes could be due to the fact that our cohort of patients are younger than those observed in other populations where the median survival is between 40 and 50 years, in contrast to the mean age of 20 years of our patients [10,11]. This is because HbF is steady in females but falls in males as the age rises, more so higher HbF in females reached significance only in the 45-49 year age group [10,12].

Different approaches have been used to predict clinical severity in sickle cell disease but most have revolved around the fetal haemoglobin level. This explains why drugs and other agents are used to increase its level. Asians who in contrast to Africans have higher HbF levels have milder clinical manifestation [2]. Prediction of severity by HbF is a subtle one, which becomes apparent when the difference in HbF values is large. In this study we have used the HbF level to assess other parameters, HbF may not have appeared to predict severity except when a comparison was made between those with HbF below and above the critical value of 7.4%, even then the differences were not statistically significant. The effect of HbF might have been more pronounced if confounding factors like alpha thalassaemia were eliminated and a larger population was studied.

There were more long survivors (those who were at least 30 years old) among patients who have HbF level of greater than 7.4%. Even though this group was less transfusion dependent, their haematocrit was not significantly different from those with HbF of less than 7.4%. Also, the rarity of vaso-occlusive crisis (bone pain crisis) was noted more among those with HbF of < 7.4% compared with those with higher HbF values.

In all but the mildest cases of sickle cell anaemia patients the spleen is eventually destroyed by multiple infarctions. Persistence of splenomegaly has been attributed to high levels of HbF and homozygous alpha thalassaemia, irreversibly sickled cell (ISC) count has also been found to be low in cases with splenomegaly. It is therefore not surprising that a palpable spleen was noted more in the group with a higher HbF level. The expected low ISC in this group cannot fully explain the fact that this group is less transfusion dependent since the steady state haematocrit remains the same in both groups.

The inability to categorically define the effect of HbF on clinical severity may explain why some patients have shown good response to drugs like hydroxyurea which increases the synthesis of HbF in sickle cell disease patients and others have not. The reason why there were more females among patients who have HbF < 7.4% is not immediately obvious. It appeared that HbF is related to patients' clinical severity. However, there is a need for more studies with a larger number of patients to study this phenomenon more closely.

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