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Sickle Cell Eye Disease in Nigerians: A study of 90 patients in Abuja

OLUFEMI BABALOLA*, CHARLES WAMBEBE

From: *Rachel Eye Centre, P. O. Box 4108, Garki, Abuja, Nigeria.
National Institute for Pharmaceutical Research and Development (NIPRD), Idu, Abuja, Nigeria.

SUMMARY

As part of the double blind cross-over phase IIb (pivot) trials on the effect of the drug NIPRISAN on the clinical morbidity of sickle cell disease (SCD). 90 patients with genotype SS (88) or SC (2) had a comprehensive eye examination, including dilated binocular indirect ophthalmoscopy. The study was carried out at the clinics of the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja. The patients had been selected on the basis of experiencing at least 3 episodes of painful crises in the preceding year. The prevalence of anterior segment signs was 11.1% for clinically apparent jaundice and 35.6% for significant corkscrew vessel formation. SCD related posterior segment signs occurred in 24%, being of the non-proliferative sickle retinopathy (NPSR) variety in 23.3% and of the proliferative sickle retinopathy (PSR) in 5.6%. Posterior segment signs (NPSR & PSR) were about twice as common in males (32.6% vs 17%, odds ratio 2.35 confidence limits $0.78 < OR < 7.22$) even though females were on average older (mean 16.3 yr. for females, 14.2 yr. for males, $p = 0.06$). The PSR rate is similar to that obtained in a Jamaican series (6%) and was seen as early as age group 10–14. It is therefore suggested that patients with SCD of the homozygous SS or SC variant from 10 years and above should have at least annual dilated fundoscopy.

INTRODUCTION

Sickle Cell Disease (SCD) has been associated with ocular morbidity and blindness since the link was first made in 1952 by Edington and Sarkies[1], as well as Henry and Chapman[2] in 1954. In 1956, Hannon[3] linked cases of vitreous haemorrhage to sickle cell haemoglobin C disease.

By 1960, Munro and Walker[4] wrote a more generalised treatise on the ocular complications of the haemoglobinopathies. Goldberg[5] proposed a classification of proliferative changes in SCD and also reported on the natural history, or stages, of the untreated disease the same year[6]. The staging proposed by Goldberg has been in use since then. However recently, Penman, et al.[7] proposed a new classification of peripheral retinal changes in sickle cell disease. It is well known that ocular complications are most often encountered in SC haemoglobin disease in spite of the fact that generalised clinical disease is worse in patients with homozygous SS disease. In fact patients with S-thalassaemia haemoglobin have more ocular complications than those with SS disease. Nigeria being the most populous back nation in the world probably has the highest incidence of SCD. Over 2 million Nigerians may suffer from SCD while another 25 million are carriers. The prevalence of HbSS in Nigeria is known to be higher in the South Western part of the country among the Yorubas where about 6% of adults are known to have this genotype and the disease was reported in 90,000 out of 5.4 million expected live births. In Eastern Nigeria, a survey of pre-school children put the prevalence of HbSS at 1.6%[8].

Nation-wide therefore, the disease causes considerable morbidity and mortality. As there is as yet no known cure while treatment is mainly supportive, the search for effective anti-sickling remedies continues. Recently the National Institute for Pharmaceutical Research and Development (NIPRD) located at Abuja in Nigeria, developed a phytomedicine from

**Author for correspondence.*

indigenous medicinal plants for the management of SCD[9]. The phytomedicine which was given the name of NIPRISAN was formulated into capsule dosage form from a freeze-dried powder of the plant parts of *Pieper guinenses, Sorghum bicolor, Eugema caryophyllum and Pterocarpus osun.* According to Awodogan and his colleagues[10] NIPRISAN did not significantly alter the functions of the kidneys and liver following acute and short term toxicity studies in rats. After obtaining mandatory approvals of NIPRD Ethics Committee and the National Agency for Food and Drug Administration (the Nigerian equivalent of FDA), clinical trials phase I and II a (pilot) were conducted. Currently, clinical trial phase IIB (pivot) is in progress.

The ocular effects of the disease in patients within the country however, needs to be more closely evaluated as studies in this area are relatively few. Osuntokun, *et al.*[11] reported on 15 patients aged between 20 to 60 with SC haemoglobin who, quite unaware of their disease, presented with primarily ocular problems. Magulike *et al.*[12] examined the eyes of 130 patients attending the paediatric sickle cell clinic of the University of Nigeria Teaching Hospital, Enugu, Nigeria. In that study, where about 99% of patients examined had the SS genotype, no case of proliferative retinopathy was found and most of them presented with mild anterior segment signs and non-proliferative posterior segment signs especially venous tortuosity. Majekodunmi and Akinyanju[13] concluded that conjunctival vessel anomalies, tortuosity of major retinal vessels and chorioretinal scars were the main ocular findings in homozygous sickle cell disease in Nigeria within their series of 124 patients in Lagos. The ongoing phase IIB double blind placebo controlled clinical trials of NIPRISAN gave another opportunity to examine a cohort of Nigerians with SCD and to evaluate the effect of the drug if any on the progression of the ocular disease. This report is on the eye findings in 90 patients participating in the trial prior to the administration of NIPRISAN.

PATIENTS AND METHODS

The studies were carried out at the clinics of the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja. Patients were included if they had electrophoresis confirmed Hb SS or SC genotype (in alkaline/acid medium), and who had experienced moderate to severe recurrent episodes and at least three painful or vaso-occlusive crises in the preceding year. The painful crises must have required treatment at a healthcare facility or at home with parenteral or equi-analgesic dose of oral narcotics or non-steroidal anti-inflammatory drugs. The crisis may include episodes of acute chest syndrome, splenic/hepatic sequestration or priapism. The patients were drawn from Abuja City and other settlements within the Federal Capital Territory. Exclusion criteria included HIV positive status, hepatitis or tuberculosis, pregnancy or lactation and patients unwilling or unable to follow instructions regarding treatment.

Most of the patients were seen within a three day period in June 1997 while others were examined by December before the commencement of dosing. In this way 90 patients were examined altogether.

Data and clinical findings of patients were entered onto a protocol designed to facilitate computerised analysis. Demographic data included name, age, sex, date of examination serial and trial numbers, genotype and treatment group. Clinical data sought included Snellen acuity with and without pinhole/glasses if worn, significant anterior segment findings including infectious conjunctivitis, vernal/allergic conjunctivitis, keratitis/corneal scar, pterygium/pinguenculum, jaundice in available daylight or white light, corkscrew vessels and others to be specified. The clarity or lack of it of the posterior segment was noted. After dilatation with mydriacyl and phenylephrine, binocular indirect ophthalmoscopy was carried out. Findings related to non-proliferative sickle retinopathy included salmon patch, preretinal haemorrhage, iridescent deposit, and black sunburst sign. Findings related to proliferative sickle retinopathy included vitreous fibrosis and the Goldberg stages of retinopathy[6]. Other retinal findings not related to SCD were also noted.

The data was entered into Borland D-Base 5.0 for windows and analysed using EPI info version 5.01a (1991).

RESULTS

Demographic profile of study population *(Figure 1)*

Of the 90 patients, 47 were female and 43 male. The average age was 15.3 years (SD 5.4) with a range between 5–36, while the modal age group was between 10 and 14 (Fig. 1). Only two of the patients (a 10-year old girl and a 14-year old boy, siblings) had the SC genotype.

Visual Acuity Profile (Table 1)

By WHO definition, acuity less than 6/18 is

regarded as visual impairment. Only two patients had best visual acuities less than 6/18 in one eye.

Eye Pathology and Signs (Table 2)

Overall, 81% of the subjects had some form of eye sign related to SCD, either in the anterior or posterior segment or both. 70% had either jaundice or corkscrew vessels while 24% had some form of SCD related posterior pathology (See tables 2 & 3, fig. 2). Of the 90 cases, 12 patients (13%) had both posterior and anterior pathology, 51(57%) had only anterior pathology and 11(12%) had only posterior pathology.

Anterior Segment Findings

28 persons had entirely normal anterior segments in both eyes and 2 others in at least one eye. Clinically evident jaundice (in available daylight) was present in 29. Corkscrew or comma shaped vessels were seen in both eyes of 48 persons and in one eye

Age/Sex Characteristics of Study Population

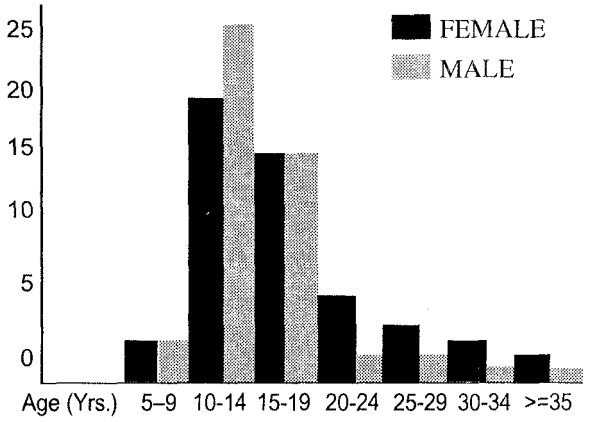

Fig 1: **NIPRISAN Clinical Trials**

Table 1: **Corrected Visual Acuity Profile in Study Population**

	Worse Eye		Best Eye	
Visual Acuity	**Frequency**	**%**	**Frequency**	**%**
6/4	67	74.4	79	87.8
6/6	12	13.3	7	7.8
6/9	8	8.9	3	3.3
6.18	1	11.1	1	3.3
6.24	1	1.1	–	–
NPL	1	1.1	–	–
Total	90	100.0	90	100.0

Table 2: **Ocular status at last visit**

Ocular Sign	No. of Patients	%
Posterior Segment Signs		
Iridescent Spots/Schisis	13	14.4
Cavities Sunburst Lesions	6	6.7
Vitreous Fibrosis	3	3.3
Salmon Patch	2	2.2
Preretinal Haemorrhage	1	1.1
Proliferative Retinopathy	5	5.6
Anterior Segment Signs		
Jaundice only	10	11.1
Corkscrew Vessels only	32	35.6
Both	19	21.1

in three others. Vernal conjunctival discoloration was present in 3 persons and there was one patient with a corneal scar in one eye. Sub-conjunctival haemorrhage was present in one eye of one person. This was apparently spontaneous but is not usually regarded as an ocular sign of SCD. There is some indication that these signs are commoner in the younger groups but this did not achieve statistical significance P = 0.37.

Posterior Segment Findings

The view of the posterior segment was unimpeded in almost all cases with adequate mydriasis. Some form of SCD related posterior pathology was present in 22 patients (24%). This was of the non-proliferative variety in 19 cases and of the proliferative in 5 cases (a combination of both in 2 cases). Vitreous fibrosis is considered a 'proliferative' sign for the purposes of this analysis. Table 2 shows the frequency of occurrence of various types of lesions. The commonest posterior segment lesion encountered were schisis cavities and/or iridescent spots, found in 13 cases (14.4%). These iridescent spots are sometimes isolated. Black sunburst lesions were present in 6 cases, vitreous fibrosis in 3, Salmon patch haemorrhage in 2 and pre-retinal haemorrhage in only 1.

Of the 5 cases of PSR in one or both eyes (a total of 7 eyes, two eyes having bilateral lesions), there were three eyes with clinically apparent vascular occlusion, 2 with arteriovenous anastomosis and one with sea fan neo-vascularisation. This latter case thus represents the most advanced PSR lesion identified in this series. The lady with the lesion was a 25-year old. The youngest patient with PSR was 14, the others

being 18, 25 and 29. Fig. 3 shows the age specific rates of SCD related posterior segment lesions. These lesions appeared from the age group 10–14 and were most frequent in patients 30 or older. The lowest frequency was however, recorded in the 20–24 years age group.

Three eyes of three cases were identified with vitreous fibrosis. All were male and aged 14, 17 and 29 respectively. The 14-year old had a co-existing A–V anastomosis in the affected eye (Stage II PSR) while the 29-year old man had clinically apparent vascular occlusion (Stage I PSR). The vitreous fibrosis was apparently isolated in the 17-year old.

Other Posterior Pathology: Maculopathy was present in 6 individuals, bilateral except in two cases, making a total of 10 eyes. This was in the form of glistening bodies in seven cases, reduced foveal reflex in one case an rough surfaced maculopathy in two. Only in the latter case was there an association with reduced visual acuity in the eye with the most advanced lesion (6/24). Other non-SCD findings were as follows. Tigroid fundus 12 eyes of 8 subjects, angioid streaks 1 eye, peripheral retinal degenerations 9 eyes of 7 patients, chorioretinal scar presumed to be due to toxoplasmosis 1, sheathed peripheral vessels 1 and Beigmerster's papilla 1.

The Influence of Sex: The frequency of all SCD related lesions in females is 83%, slightly higher than 81% for males. (Odds ratio 0.90, confidence limits $0.27 < \text{or} < 3.03$). When only anterior segment lesions are considered, 70.2% and 69.7% of females and males are affected respectively, again showing an almost equal distribution. (Odds ratio 0.95, c.l. $0.35 < \text{or} < 2.60$). However, when only posterior segment lesions are considered, almost twice as many males are affected. (17% females, 32.6% males, Odds ratio 2.35 c.l. $0.78 < \text{or} < 7.22$).

DISCUSSION

The assessment of the posterior lesions of SCD is enhanced with the use of fluorescent angiography and the fact that this was not used in this study makes it difficult to be certain that all cases of vascular occlusion, arterio-venous anastomosis or more advanced neovascular lesions have been identified. It can be assumed therefore that cases of PSR may have been under-reported in this series. Also it must be said that this cohort is somewhat enriched because of the selection criteria (at least three painful vaso-occlusive crises in the preceding year). Hence although SCD related posterior segment signs (including proliferative and non-proliferative disease) was present in about 1 in 4 of the patients, this should be extrapolated to the general SCD population with caution. This may explain why no case of proliferative disease was found in the Enugu study[12] in which 130 consecutive cases attending the paediatric SCD clinic were examined. Venous tortuosity, which was the mainly reported sign in that study, (30 of 130 cases) was not systematically recorded in our study because of its non-specific nature, and the fact that it is not pathognomonic of SCD retinopathy. However, one case of the black sunburst sign was recorded in the Enugu study.

The prevalence of proliferative disease (5 of 90 cases, i.e. 5.6%, 88 of whom are SS) is similar to the findings of Fox *et al.*[14] in Jamaican patients who are homozygous for SS disease (25 of 328 patients at first examination, 6%). In that study, it was again confirmed that PSR was more prevalent in the SC population, (i.e. 32%). However, no retinopathy was found in the two patients, who were in fact siblings, with SC genotype in this study. Vitreous fibrosis represents a progression of pre-retinal haemorrhage. In essence it may be considered a 'proliferative' lesion on the same level of evolution as vitreous haemorrhage except that it does not eventuate from neovascularisation. However, it can also progress to retinal break and detachment.

The non-proliferative signs which were seen in 19 of the 90 patients were quite significant. Most of these signs are now known to result from intra-retinal haemorrhage, the black sunburst sign due to bleeding close to the pigment epithelial layer and the salmon patch haemorrhage occurring more superficially at the inner nuclear layer, while Schisis cavities are associated with bleeding in the outer plexiform layer. The latter are the commonest non-proliferative lesions encountered in this study.

Visual loss was uncommon in this cohort. Only two patients had visual impairment. The first, a 12-year old boy, had an acuity of 6/24 in the right eye and 6/4 in the fellow eye. A maculopathy was present in both eyes, worse in the right. This was a dry, rough surface type of maculopathy but it is not clear if this is directly attributable to the SCD. However, angioid streaks were present in the right eye as well, while a sunburst lesion was noted in the left. The other patient, a 17-year old boy had a right empty socket having had an enucleation in that eye following a bicycle spoke injury in 1985. He expectedly had no

perception of light in that eye but the other eye was normal at 6/4. Other posterior pathology of interest included angioid streaks which may also be associated with SCD but it must be emphasized that they are not pathognomonic. Tigroid fundal appearance may mask the presence of salmon patches, and on at least four occasions, this appeared to be the case. However, the doubt was resolved in favour of an absence of the lesion.

It is interesting that SCD related posterior segment lesions were almost twice as common in males. This is in line with the findings of Fox *et al.*[14] in which it was found that PSR was commoner in males especially in SC disease but also in SS disease, although the analysis in that study excluded non-proliferative disease. In the present study the odds ratio that males would have retinopathy compared to females was 2.35 confidence limit 0.78 < or < 7.22 Fox *et al.*[14] linked the higher risk in males to haematological variables, showing significant associations of PSR with high Hb in SS males. Haematological data was available in 66 of our patients. The mean Hb at baseline for males was slightly higher at 9.62 than that of females at 9.53 but this difference did not achieve statistical significance (F statistic = 0.02, p = 0.88). The fact of male preponderance is all the more striking because the average age of the females in this study (16.3 yr) is higher than in males (14.2yr.), p = 0.06, while the risk of peripheral retinal vaso-occlusion is known to increase with age. It has to be stated however that the relationship between these haematological variables and the risk of retinopathy is neither straight forward nor simple. It varies with the genotype (SS vs SC), the sex and whether vaso-occlusion or proliferative disease alone is being considered. For instance, the Jamaican cohort study[15] found that in SS disease, closure was associated with a low, rather than a high Hb in males only while low foetal haemoglobin was associated with PSR in both sexes. PSR in SC disease was associated with a high Mean Cell Volume and a low foetal Hb in females. It seems plausible that factors other than the haematological ones may be adduced to account for the sex difference.

On the issue of age, this study showed that the age specific rates of all SCD related posterior pathology were highest in patients thirty years and above, and that these lesions first appeared in the 10–14 years of age bracket. The youngest patient with PSR was 14. In the series of Fox *et al*[14], PSR was first observed in the 15–19 years age group in SS disease and earlier in the 10–14 years age group in SC disease. The apparent drop in the rate for the 20–24 years age bracket may be due to the small size of the sample.

If it is remembered that all those with PSR are at risk of blindness from tractional retinal detachment and/or vitreous haemorrhage, it can be safely recommended that SS and especially SC patients should have at least an annual eye examination including dilated binocular indirect ophthalmoscopy after the age of ten. A similar recommendation has been made by Kimmel *et al*[16] who emphasized the importance of ophthalmic examination in teenage sickle cell patients to detect and treat proliferative disease.

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