

ORIGINAL ARTICLE

Ocular manifestations of sickle cell disease at the Korle-bu Hospital, Accra, Ghana

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PURPOSE. To determine the magnitude and pattern of ocular manifestations in sickle cell disease at Korle-bu Hospital, Accra, Ghana.

METHODS. Hospital-based cross-sectional study including all patients with sickle cell disease reporting for routine follow-up at the Sickle Cell Clinic at Korle-bu Hospital, Accra, Ghana.

RESULTS. A total of 201 patients with sickle cell disease (67 male and 134 female) were enrolled, comprising 114 subjects with genotype HbSS, aged 6-58 years, mean 19.26 (SD 11.70), and 87 with genotype HbSC, aged 6-65 years, mean 31.4 (SD 16.76). Visual impairment was found in 5.6% of eyes examined. Causes were cataract, proliferative sickle retinopathy (PSR), optic atrophy, phthisis bulbi, and central retinal artery occlusion. Common anterior segment signs of sickle cell disease, which were more common in HbSC patients, were tortuous corkscrew conjunctival vessels, iris atrophy, and cataract. Eyes with iris atrophy or depigmentation were 1.8 times more at risk of PSR than eyes without. Overall, PSR was found in 12.9% of subjects examined (3.5% of HbSS, 25.3% of HbSC; 15.9% of males and 11.2% of females). The prevalence of proliferative sickle retinopathy increased with age and increased systemic severity of sickle cell disease; sex did not have an influence.

CONCLUSIONS. There is a high prevalence of ocular morbidity in sickle cell disease patients at Korle-bu Hospital. Prevalence increased with age, systemic severity of sickle cell disease, and HbSC genotype.

KEY WORDS. Epidemiology, Ocular manifestations, Public health, Sickle cell disease, Sickle cell retinopathy

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INTRODUCTION

Sickle cell hemoglobinopathies are a group of inherited diseases characterized by an abnormality in the β -chain of the hemoglobin molecule. Sickle cell disease (SCD) is found all over the world except in the Far East and in the Arctic countries. It is most common in Africans and people of African descent but also occurs in the non-black population of Saudi Arabia and India. The chief manifestations are

chronic hemolytic anemia and vaso-occlusive crises that cause severe pain as well as long-term and widespread organ damage (1, 2).

The eyes offer a unique opportunity for direct observation of the vaso-occlusive process in SCD (2, 3). The conjunctiva in sickle cell patients shows tortuous "corkscrew" conjunctival vessels, transient saccular dilatation of vessels, and multiple, short, comma-shaped capillary segments seemingly isolated from the vascular network (2).

The SS genotype form exists in 0.4% of the black population and causes severe systemic but mild ocular disease, while the less common SC and S β -thal genotypes cause mild systemic but severe ocular disease (4). The prevalence of SC and S β -thal varies between different black populations. West Africa has the highest prevalence of HbSC in Africa (2). An estimated 1%-2% of Ghana's approximately 25 million people have SCD, with a relatively high prevalence of the hemoglobin C gene (1% of the Ghanaian population) (2). However, the prevalence and pattern of ocular morbidity due to sickle cell disease in Ghana is unknown. In order to plan ocular screening programs, data on the influence of age, sex, and genotype on ocular morbidity in Ghanaian SCD patients are needed. Such information is currently unavailable, though workers in neighboring Togo found an increased prevalence of proliferative sickle retinopathy (PSR) with increasing age (5). Proliferative sickle retinopathy has also been found to be more common in males, to increase with age in both genotypes, and to have a tendency of being bilateral (6).

It would be useful to know the risk of PSR in Ghanaian SCD patients with abnormal anterior segment signs, since anterior segment examination is technically easier to perform than funduscopy and therefore easier to teach to personnel who might be recruited for an ocular screening program in a resource-poor setting.

Patients with PSR in Ghana usually present late to the ophthalmologist with vitreous hemorrhage or retinal detachment. This, coupled with the unavailability of a specialized vitreo-retinal surgery unit in Ghana, makes the early detection of PSR very important. Our study aims at determining the magnitude and pattern of ocular manifestations in SCD patients at Korle-bu Hospital in Accra, Ghana. It is thus important in several respects. It provides data needed for the development of an appropriate protocol for screening and management of PSR, encouraging a multidisciplinary approach in the management of SCD. Involving ophthalmologists in the care of SCD patients has become increasingly important as the expansion of appropriate health care services worldwide enables most sickle cell patients to live into adulthood, allowing their ocular changes to become manifest.

MATERIALS AND METHODS

This hospital-based cross-sectional study was carried out at the Sickle Cell Clinic (SCC), Korle-bu Hospital, Accra,

Ghana, from March 4 to April 3, 2007. The SCC is a unit in the Department of Medicine dedicated to the management of SCD patients. Sickle cell patients reporting for routine follow-up for SCD at the SCC older than 6 years of age were eligible for this study. Following written informed consent, 201 consecutive patients were recruited. Clinical and demographic data were obtained by a structured questionnaire administered by the first author and using information from the hospital records. Dependent variables included age, sex, and genotype. The estimated number of admissions due to sickle cell crisis was used as an indicator for severity of systemic disease. Vision with the patients' own correction or pinhole-corrected visual acuity was assessed with a Snellen chart and E chart. Ocular alignment, extraocular motility, and pupillary light reflex were assessed for possible neurologic deficits as well as pupillary reactions using a pen torch. Anterior segment slit-lamp biomicroscopy and, in cooperative patients, applanation tonometry was carried out. Anterior segment examination was performed to assess the presence or absence of signs due to SCD in the conjunctiva, cornea, anterior chamber, pupil, iris, lens, and anterior vitreous. Afterwards, dilated examination of the ocular fundus was done using indirect binocular ophthalmoscopy. Fundus findings were documented with standard retinal drawings.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) for Microsoft Windows, using Fisher exact test and chi-square test.

RESULTS

A total of 201 subjects were included in the study. The age, sex, and genotype distribution of subjects is shown in Table I. All patients had normal vision with their own correction or with pinhole in the better eye. In patients with HbSS genotype, 2/228 (0.9%) eyes had abnormal visual acuity, compared to 8/174 (4.6%) HbSC eyes. The difference in the number of visually impaired eyes in the 2 genotypes was statistically significant ($p=0.02$, cross tab, Fisher exact test), with more visually impaired eyes in the HbSC genotype (Tab. II).

The reasons for vision loss in patients with visual impairment were cataract, vitreous hemorrhage, optic atrophy, phthisis bulbi, central retinal artery occlusion, and sea-fan neovascularization. Some eyes had more than one reason for vision loss. Intraocular pressure was below 21 mmHg

TABLE I - AGE, SEX, AND GENOTYPE DISTRIBUTION OF SUBJECTS

Age range, years	Sex				Genotype			
	Male		Female		HbSS		HbSC	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
6-15	34	(16.9)	34	(16.9)	51	(25.4)	17	(8.5)
16-25	13	(6.3)	40	(19.9)	33	(16.4)	20	(10.0)
26-35	14	(7.0)	21	(10.4)	21	(10.4)	14	(7.0)
36-45	2	(1.0)	17	(8.5)	5	(2.5)	16	(8.0)
46-55	3	(1.5)	16	(8.1)	3	(1.5)	16	(8.0)
56-65	1	(0.5)	6	(3.5)	1	(0.5)	6	(3.0)
Total	67	(33.2)	134	(67.3)	114	(56.7)	87	(44.5)

TABLE II - VISION WITH THE PATIENTS' OWN CORRECTION OR WITH PINHOLE (N=402 EYES)

Visual acuity	SS n (%)	SC n (%)
Normal vision	225 (99.1)	165 (95.3)
Visual impairment	0	5 (2.9)
Severe visual impairment	0	1 (0.6)
Blind eyes	2 (0.9)	2 (1.2)
Excluded eyes	1	1
Total	228	174

in all but 6 subjects (3 HbSS and 3HbSC). The clinical findings sorted by genotype are shown in Table III. Tortuous, corkscrew conjunctival vessels, iris atrophy, and cataract were significantly more common in the HbSC genotype ($p=0.018$, 0.002 , and 0.003 respectively). Jaundice was more common in the HbSS genotype ($p=0.005$). The average age of patients with cataract was 39.9 years (SD 15.4) (range 32- 65). The black sunburst sign and sea-fan neovascularization were significantly more common in genotype HbSC ($p<0.001$). Sea-fan neovascularization was seen

TABLE III - CLINICAL SIGNS VERSUS GENOTYPE (N=201 SUBJECTS: 114 SS, 87 SC)

Anterior segment signs	SS (n=114) n (%)	SC (n=87) n (%)	Total (n=201) n (%)	p value
Conjunctiva				
Tortuous corkscrew conjunctival vessels	53 (46.5)	55 (63.2)	108 (53.7)	0.018*
Saccular dilatations of vessels	45 (39.5)	42 (48.3)	87 (43.3)	0.212
Seemingly isolated cap segments	42 (36.8)	39 (44.8)	81 (40.3)	0.253
Injection	0	2 (2.3)	2 (1.0)	—
Jaundice	10 (8.8)	0	10 (5.0)	0.005*
Iris and lens signs				
Iris depigmentation	40 (35.1)	39 (44.8)	79 (39.3)	0.161
Iris atrophy	4 (3.5)	14 (16.1)	18 (9.0)	0.002*
Rubeosis	0	0	0	—
Cataract	3 (2.6)	12 (13.8)	15 (7.5)	0.003*
Nonproliferative fundus signs				
Increased tortuosity of major retinal vessels	7 (6.1)	1 (1.1)	8 (4.0)	0.072
Pale peripheral retina	24 (21.1)	27 (31.0)	51 (25.4)	0.112
Salmon patch hemorrhage	4 (3.5)	4 (4.6)	8 (4.0)	0.702
Black sunburst sign	9 (7.9)	24 (27.6)	33 (16.4)	<0.001*
Angioid streaks	6 (5.3)	6 (6.9)	12 (6.0)	0.636
Central retinal vein occlusion	0	1 (1.1)	1 (0.5)	—
Central retinal artery occlusion	0	0	0	—
Proliferative fundus signs				
Sea-fan neovascularization	4 (3.5)	22 (25.3)	26 (12.9)	<0.001*
Vitreous hemorrhage	2 (1.8)	3 (3.4)	5 (2.5)	0.449
Retinal detachment	1 (0.9)	1 (1.1)	2 (1.0)	0.851

*Significant.

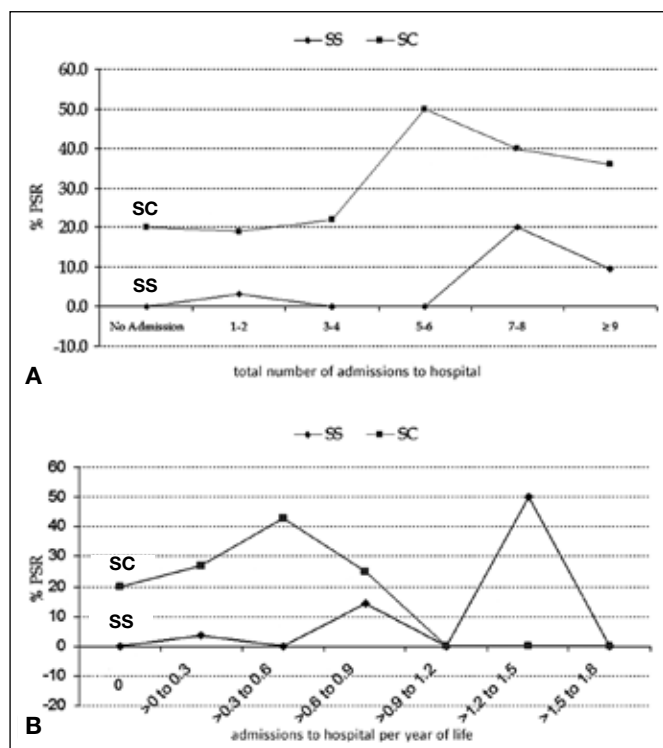


Fig. 1 - The relationship between the percentage of proliferative sickle retinopathy and (A) the total number of admissions to hospital and (B) the number of hospital admissions per year of life. An increasing frequency of admission to hospital in HbSS patients correlates with a higher rate of proliferative sickle retinopathy. PSR = proliferative sickle retinopathy.

in 26 subjects (12.9%), 22 HbSC and 4 HbSS ($p < 0.001$); 15.9% were male and 11.2% female ($p = 0.392$). It increased with age, occurring in 1 (aged 10 years, male, HbSS) out of 68 children, compared to 25/133 adults ($p = 0.001$) with 2/7 in the age group 56-65 years affected. Vitreous hemorrhage occurred in 5 subjects with SN 2/233 HbSS and 3/169 HbSC, 1/67 male and 4/134 female ($p = 0.480$), with prevalence increasing with advanced age. Retinal detachment was found only in 2 female patients. Category-based prevalence of PSR in different categories of sickle cell patients is shown in Table IV.

Other findings were peripheral retinal pallor and salmon patch hemorrhages. Although 50% of children had pale retinas, which may have been due to anemia, only 1.6% had PSR. The black sunburst sign, found in 16.4% of subjects, was significantly more common in HbSC (27.6%) than HbSS (7.9%) subjects ($p < 0.001$) and increased with age.

The prevalence of PSR increased with increasing total number of admissions to the hospital, for both genotypes, as shown in Figure 1A. The prevalence of PSR first increases, and then decreases, with increasing admissions per year of life in HbSC patients, but increases with increasing admissions per year of life in HbSS patients, as shown in Figure 1B. These results suggest that the number of admissions to the hospital might not be of predictive

TABLE IV - CATEGORY-BASED PREVALENCE OF PSR IN DIFFERENT CATEGORIES OF SICKLE CELL PATIENTS

Subgroup selected for analysis	Percentage PSR
Total subjects (n=201)	12.9
SS subjects only (n=114)	3.5
SC subjects only (n=87)	25.3
Children only (n=68)	1.5
Adults only (n=133)	18.8
SS adults only (n=63)	4.8
SC adults only (n=70)	31.4
SS adults only, with admission (n=54)	5.6
SS adults only, with no admission (n=9)	0
SS adults only, with admissions per year >0.3 (n=16)	12.5
SS adults only, with admissions per year >0.6 (n=8)	25.0
SS adults only, with admissions per year ≤0.6 (n=55)	3.6

PSR = proliferative sickle retinopathy.

value in HbSC patients, while an increasing frequency of admission to the hospital in HbSS patients correlates with a higher rate of PSR. Eyes with iris atrophy or depigmentation were 1.8 times more at risk of PSR than eyes without (odds ratio 1.8).

DISCUSSION

In this study, the number of subjects enrolled declined with increasing age, with 68 subjects (33.8%) in the age group 6-15 years and only 7 subjects (3.5%) in the age group 56-65 years. This may reflect the lower life expectancy of sickle cell patients when compared with the general population in Ghana (male 59.5 years, female 60 years). However, other factors such as reduced mobility of older patients might also contribute to these findings.

Our study supports other authors' reports that bilateral visual loss from SCD is rare (7). We found visual impairment in only 2.5% of eyes at presentation, with all patients having normal corrected vision in the better eye. While unilateral loss of vision from SCD is not of serious public health significance, it is significant for the individual patient who lives in fear of losing vision in the better eye. Visual loss was more frequent but less severe among HbSC patients (proliferative and nonproliferative retinal changes) than HbSS patients (anterior segment ischemia and central retinal artery occlusion/central retinal vein thrombosis).

In our study, only 63% of patients showed conjunctival signs, which is a low rate compared to data from Kenya (87%) and Nigeria (77%-81%) (2, 8). Cataract and iris atrophy or depigmentation were 3 times more common among HbSC than HbSS subjects. In sickle cell patients, cataracts occurred at a younger age (mean 39.9 years, range 32-65) than in the general population. We found a well-regulated intraocular pressure in almost all patients, without any glaucomatous optic disc changes. In accordance with other studies, increased tortuosity of major conjunctival vessels was the most common sign (9, 10). It was significantly more prevalent in HbSS subjects ($p=0.018$) and in females, the youngest being 12 years old. Our 4.0% prevalence of salmon patch hemorrhage is less than the 6.4% seen in Nigerian patients (3). Similar to the findings of this Nigerian study, the presence of the black sunburst sign was dependent on the genotype (HbSC>HbSS) and increasing age of the patients (3).

The prevalence of PSR varies in different countries depending on the life expectancy of SCD patients and genotype. Preva-

lence of PSR in Kenya was 1%, Saudi Arabia 1.6%, Nigeria 5.6%, Togo 9.4%, Jamaica 24%, and United States 18% (5, 11-14). Our 12.9% prevalence of PSR (sea-fan neovascularization with or without vitreous hemorrhage and retinal detachment) is comparable to Nigeria and Togo, while life expectancy of HbSS and HbSC populations in these countries is similar. In Kenya and Saudi Arabia, the HbSS population dominates, while Jamaican and American SCD patients survive longer. PSR was significantly more common in HbSC (25.3%) than HbSS (3.5%) subjects ($p<0.001$), with a male:female ratio of 15.9%:11.2% ($p=0.392$), and increased with age ($p=0.001$). However, Fox et al found a statistically significant higher prevalence of PSR in males (6). Only 1.5% of children <15 years had SN compared to 28.6% of patients 56-65 years of age. Our SN prevalence in the other age groups was similar to the findings of Balo et al in Togo (5). This was not surprising, given that the 2 countries share similar populations, genotypes, and life expectancy. With regard to vitreous hemorrhage, out of the 5 patients concerned (2.5%), 2 (1.8%) were HbSS and 3 (3.4%) HbSC subjects. For HbSS subjects, our prevalence is higher than the one in Kenyan subjects (0%), but less than the 3.8% found in Nigerian HbSS subjects (3, 10). Our 3.4% prevalence in HbSC patients is much lower than the 10%, 8%, and 18% found by authors in Senegal, Togo, and Curacao (5, 7, 15). Retinal detachment was seen in 2 (1%) subjects, more than the 0% found in Kenya and Nigeria but lower than the 8% prevalence in Curacao, which might be explained by the higher PSR prevalence there (3, 4).

Statistically, our findings on the relationship between iris atrophy/depigmentation and the development of PSR are inconclusive, but we noted that the eye with the severest atrophy also had the most florid SN. This may indicate that the increased risk of having PSR might be related to the severity of iris atrophy rather than just its presence, as Acheson et al (16) found that iris atrophy was closely associated with PSR in the same eye. For the patients with HbSC, admission history seems not to be predictive of PSR based on the distribution pattern in Figure 1B. However, for patients with HbSS, there was a positive correlation between PSR and the systemic severity of sickle cell based on admission to hospital history.

Our study shows that the risk of development of PSR increased with the total number of admissions to hospital (an index of systemic severity of SCD) for both genotypes. This number is in turn related to age; older patients are likely to have more admissions, but their increased prevalence of PSR may be more related to age than to the number of admissions. However, the power of this correlation between systemic severity and PSR

is low because of the relatively low number of eyes with PSR in our study. Kent et al (17) found no correlation between the systemic complications of SCD and PSR.

The risk of developing PSR in SCD patients was not evenly spread throughout our study population. While the overall prevalence was 12.9%, it varied with different subgroups. HbSC adults had the highest prevalence of PSR (31.4%). Overall PSR prevalence in HbSS patients was 3.5%, but it was 25.0% in adults with admission per year of life >0.6.

In an environment with limited resources, our analysis supports a PSR screening program which should consider HbSS adults with admissions per year >0.6 and all HbSC adults. This protocol would leave out children, who have a PSR prevalence of 1.5%, and HbSS adults with admission per year of life ≤0.6, who have a PSR prevalence of 3.6%. However, all sickle cell patients with frank iris atrophy on anterior segment examination should have a screening funduscopy to rule out PSR.

In this study, we examined the eyes of 201 SCD patients with an overall PSR prevalence of 12.9%. Of 70 HbSC adults examined, 22 had PSR. Of 8 HbSS adults with admission per year >0.6 examined, 2 had PSR. By applying the screening protocol as described above, only 78 of 201 patients, i.e., about 40%, would have to be examined and 24 out of the 26 PSR subjects would be diagnosed. Only 2 out of the 26 subjects with PSR (2 HbSS subjects) would not have been diagnosed correctly. However, the risk of blindness for these 2 patients is still very low due to the higher rate of a self-limiting course of disease in HbSS patients.

Although vision loss is uncommon in SCD, it is very important to those who end up with reduced visual acuity. Therefore, preventive measures are important to minimize this risk. This study gives data that support the development of a screening protocol for PSR in Accra with the focus on HbSC adults and HbSS adults with previous admissions due to sickle cell crisis in order to improve the early detection and management of PSR in Ghana.

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