Original Article

Sickle Cell Retinopathy: Patient Awareness, Mode of Presentation, and Treatment Modalities in Ibadan, South-West Nigeria

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Abstract

Background: Sickle cell retinopathy is a recognized complication of sickle cell disease (SCD) which may lead to visual impairment or blindness. Despite this, many patients with SCD hemoglobinopathy SC and SS are unaware of their genotype, hence resulting in only occasional or no eye checks with possibilities of getting blind. **Purpose:** The purpose of this study was to describe the genotype awareness, pattern of presentation, and treatment of sickle cell retinopathy in Ibadan. **Methods:** This was a retrospective review of the case notes of 64 patients with the diagnosis of sickle cell retinopathy seen over two years (January 2018 to December 2019). Sociodemographic characteristics, clinical data, ophthalmic assessment, and treatment performed on patients were extracted onto pro forma. Information obtained included age, sex, sickle cell genotype, genotype awareness from their medical history, retinal findings using Goldberg classification, and treatment modalities for the patients. Data analysis was performed using the IBM SPSS software version 22. Analysis was done using proportions and percentages. **Results:** Medical records of 64 patients were reviewed. The mean age of the patients was 39.05 ± 10.48 (range: 20–65) years, with a male-to-female ratio of 1.8:1. Sixty (93.8%) patients had genotype SC. Forty-six (71.8%) patients were aware of their genotype. Fifty-six patients presented with Proliferative sickle cell retinopathy (PSR) in the right eye, while 55 had PSR in the left eye. These spanned all the different grades of PSR. Treatment offered at the first visit included laser photocoagulation, intravitreal anti-vascular endothelial growth factor (bevacizumab), vitrectomy, and scleral buckle. At subsequent follow-up visits, detailed ocular examination on patients was done to look out for new/active lesions. If any of these lesions were found, repeat or additional treatment was offered to help stabilize and/or improve the best-corrected visual acuity of patients. **Conclusion:** This study has demonstrated high genotype awareness among the studied patients. Despite this high awareness, majority of our patients presented with varying stages of proliferative sickle cell retinopathy. While our patients had more than one type of treatment, some defaulted due to lack of funds. Therefore, to improve the quality of life of SCD patients, it is essential for health-care providers and other stakeholders to design policies for sustainable and accessible eye care programs to avoiding needless blindness from sickle cell retinopathy.

Keywords: Anti-vascular endothelial growth factor, blindness, genotype, laser photocoagulation, sickle cell retinopathy

Introduction

Sickle cell disease (SCD), the most common hematological disease,[1] is an autosomal recessive genetic disorder that causes alteration in the β-globin chain.[2,3] This alteration leads to a replacement of glutamic acid by valine at the sixth position of the ß-globin chain, thus producing anomalous hemoglobin (Hb).[4] Among the numerous variants of anomalous Hb genotypes that have been discovered, Hb SS and Hb SC are found to have high occurrences in Africa.[5] It is estimated that among the over 330,000 children born with Hb diseases globally, about 83% of them have SCD.[6] Diallo[7] also stated that among the babies born in Africa each year, about 200,000 have SCD. Despite this high prevalence of SCD among Africans, genotype awareness has been reported to be poor in various studies across Nigeria.[8-11] In addition to the poor genotype awareness, other studies[11-13] also reported

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reduced knowledge of the methods of inheritance of SCD, its accompanying symptoms, and management.

Hb SC is responsible for majority of ocular involvement when compared with other hemoglobinopathies like Hb SS.[14-17] One of the major pathways identified is the vaso-occlusive event that occurs along the vascular system of the eye.[18] This occlusion leads to a series of events that causes hypoxia and ischemia of ocular structures, thereby resulting in various pathological changes which may include proliferative and nonproliferative retinopathies.

In proliferative sickle cell retinopathy (PSR), the lesions develop mostly in the retinal periphery between the perfused and nonperfused areas. These lesions, usually asymptomatic in the early stages of the disease process owing due to their location, are a major cause of vision loss in advanced stages. With these lesions in mind, Goldberg in 1971 offered a classification system[19] that has enhanced the management of retinal complications arising from hemoglobinopathy SC or SS. He characteristically defined PSR into five stages. These include (1) Peripheral arterial occlusion, (2) peripheral arteriovenous anastomosis, (3) peripheral retinal neovascularization (sea-fan), (4) vitreous hemorrhage, and (5) retinal detachment.

The treatment approach in proliferative sickle cell retinopathy is based on treating any active sea-fan neovascularization before it results in vitreous hemorrhage and/or retinal detachment.[20,21] Laser photocoagulation has been the treatment of choice for Stage 3 PSR.[22-24] This method of treatment obliterates new vessels, thus preventing visually threatening complications such as vitreous hemorrhage and retinal detachment.[25] In cases of advanced cases of PSR, other methods of treatment include pars plana vitrectomy,[26,27] scleral buckling,[26] and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection.[28,29]

Individuals with Hb SC, unlike those with Hb SS, have fewer associated systemic complications, which makes them generally physically healthier and enables them to live longer.[30] In addition, recent advances in the field of medicine have enabled individuals with SCD to live longer, even into late adulthood. The increased life span makes them likely to develop related long-term complications involving the eyes, bones, and other body organs.

These developments have important implications. First, the complications of SCD are expected to keep rising in decades to come as SCD patients are living longer due to advancements in health care.[31] Second, the expected upsurge of associated ocular complications in addition to other comorbidities will negatively affect the already fragile health system.[32] Therefore, to curb the rise of ocular complications of SCD, there should be mass education of people on their genotype awareness and those with Hb S be advised on the need for routine eye screening. Furthermore, there should be provision of an accessible and affordable comprehensive health-care system for those that will be needing specialized health care. All these put together would go a long way in reducing needless blindness from ocular complications of PSR.

This study was carried out to present the genotype awareness and the pattern of presentation and describe the treatment of sickle cell retinopathy in Ibadan.

Methods

A retrospective review of the retina registers of cases presenting to the retinal outpatient clinic of the University College Hospital, Ibadan, was done. Sixty-four case notes of patients with diagnosis of sickle retinopathy over the last two years (January 2018 to December 2019) were identified and retrieved. Sociodemographic, clinical data, ophthalmic assessment, and treatments performed on patients were retrieved and recorded in pro forma. Information obtained and recorded included age, sex, diagnosis, genotype awareness from their medical history, retinal findings, and treatment modalities for the patients.

Clinical diagnosis of sickle cell retinopathy was made following biomicroscopic examination using Haag-Streit BM 900 slit-lamp biomicroscope with a +78D stereoscopic noncontact lens (Volk Optical, Inc. Ohio) and binocular indirect ophthalmoscopy (Appasamy AAIO wireless; Appasamy Associates, Chennai, India) with +20D lens (Volk Optical, Inc. Ohio) after pupillary dilatation with guttae tropicamide 1% and phenylephrine 2.5%. Fluorescein angiography, ocular ultrasound, and optical coherence tomography were requested for confirmatory diagnosis.

Pattern of presentation of ocular findings was determined from retinal findings based on examination and diagnosis. These findings were then graded using Goldberg classification.[19] Treatment was offered based on clinical findings with/without a confirmatory diagnosis. At subsequent follow-up visits, patients had dilated indirect ophthalmoscopy to assess the effect of previous treatment or areas of active disease.

Data were analyzed using the Statistical Package for the Social Sciences IBM (SPSS-IBM), version 24 (SPSS Inc., Chicago, Illinois, USA), and reported as frequency distributions and percentages. The study obeyed the tenets of Helsinki. Consent was obtained from the patients before the fundus pictures were taken.

Results

A total of 64 patients with sickle cell retinopathy were reviewed, consisting of 41 (64.1%) males and 23 (35.9%) females (ratio of 1.8:1). The mean age of the patients was 39.05 ± 10.48 (range: 20–65) years. Age and sex distribution are shown in Figure 1. The genotypes of patients seen include 60 (93.8%) cases of Hb SC, 3 (4.7%) cases of Hb SS, and 1 (1.6%) case of Hb CC. Twenty-six (40.6%) patients seen in our clinic resided in Oyo state, in which our center is

located, while 38 (59.4%) resided in other parts of the country. Forty-six (71.8%) patients knew their genotype at presentation.

Twenty-five and 23 patients presented blind (best-corrected visual acuity [BCVA] <3/60) in the right and left eyes, respectively. After treatment, this reduced to 11 patients and 14 patients in the right and left eyes, respectively. BCVA of patients at presentation and posttreatment is presented in Figure 2.

Various sickle cell retinopathies were seen in this study, as demonstrated in Table 1. Fifty-one (79.7%) patients had bilateral sickle cell retinopathy and 13 (20.3%) had unilateral involvement at presentation. The stages of proliferative SCR as seen in our patients at diagnosis are presented in Table 2. Furthermore, some fundus pictures of patients are shown in Figure 3.

Treatment modalities offered to the patients were either conservative or interventional. Conservative treatment included advising patients to sleep with two pillows and avoiding medications like nonsteroidal anti-inflammatory drugs that may worsen the vitreous hemorrhage. Interventional treatment included pars plana vitrectomy, retinal laser photocoagulation, intravitreal anti-vascular endothelial growth factor, and scleral buckle surgery depending on the stage of proliferative sickle cell retinopathy (PSR) at initial presentation and follow-up. Patients that had nonproliferative sickle cell retinopathy and Stage 1 and 2 proliferative sickle cell retinopathies were followed up with no initial intervention. Forty-six eyes (right eye –19 and left eye –27) that had either Stage 3 PSR or retinal tears from fibrovascular lesion underwent barrage laser photocoagulation as first line of treatment, while 27 eyes had laser photocoagulation as second line of treatment. Eight eyes with non-resolving vitreous hemorrhage and/or retinal detachment had vitrectomy alone, while five eyes had vitrectomy with anti-VEGF. However, ten patients with combined retinal detachment who could not afford vitrectomy had scleral buckle surgery.

Furthermore, eight eyes of patients with grade IV proliferative sickle cell retinopathy received intravitreal bevacizumab as first line of treatment, while two eyes had intravitreal bevacizumab as second line of treatment. Interventional treatment of the patients is represented in Table 3.

Table 1: Fundus findings of patients

	Frequency (%)	
	Right eye	Left eye
Proliferative SCR	56 (86.2)	55 (86)
Nonproliferative SCR	2 (3.1)	1 (1.6)
Mixed	1 (1.5)	4 (6.2)
Nil	5 (7.7)	2 (3.1)
No view	-	2 (3.1)
Total	64 (100)	64 (100)

SCR: Sickle cell retinopathy

Table 2: Stage of proliferation

Stage of proliferative SCR	Frequency (%)	
	Right eye	Left eye
1	2 (3.5)	1 (1.7)
2	3 (5.3)	5 (8.5)
3	32 (56.1)	36 (61)
4	16 (28.1)	14 (23.7)
5	4 (7)	3 (5.1)
Total	57 (100)	59 (100)

SCR: Sickle cell retinopathy

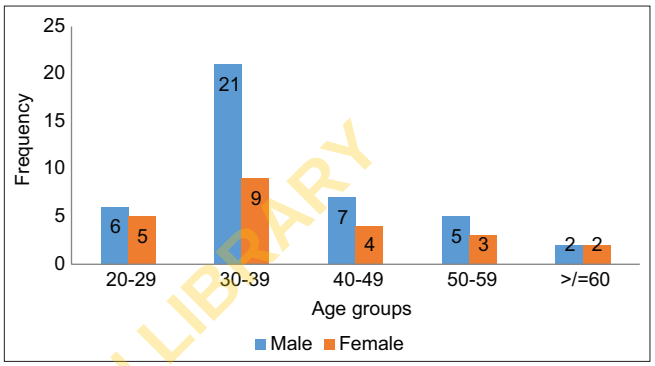

Figure 1: Age and sex distribution of patients

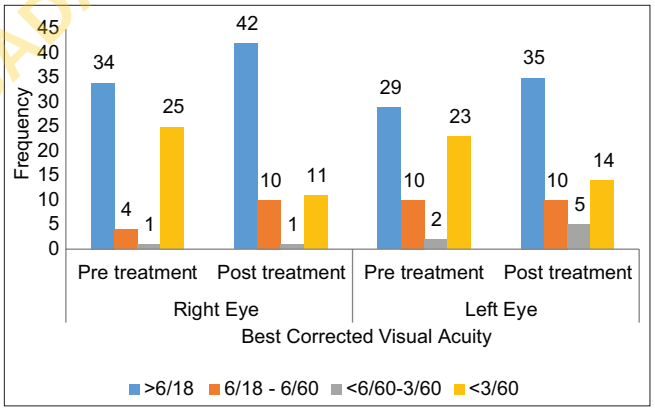

Figure 2: Pretreatment and posttreatment visual acuity of patients

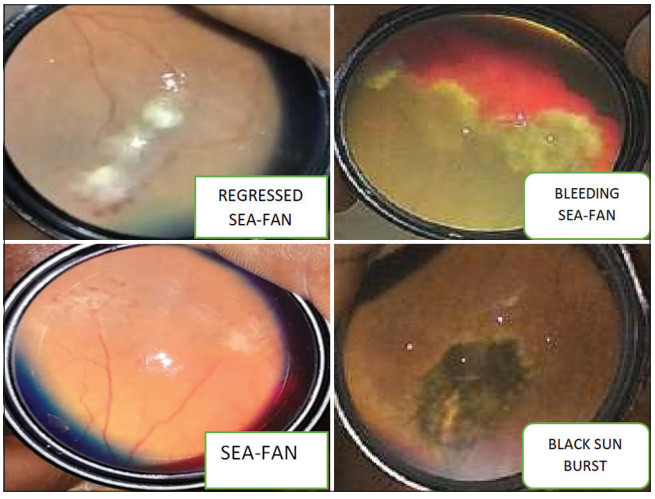

Figure 3: Sickle cell retinopathies in Ibadan

Table 3: Intervention treatment of patients

	First treatment (eyes)	Repeat treatment (eyes)
Vitrectomy	8	2
Intravitreal bevacizumab (1.25 mg/0.05 ml)	8	2
Vitrectomy + anti-VEGF	5	-
Scleral buckle	10	2
Laser photocoagulation	46	27

VEGF: Vascular endothelial growth factor

Discussion

The mean age of the patients was 39.05 ± 10.48 years (range: 20–65 years) in our study. The peak age group was between 30 and 39 years of age. This is similar to a previous report in our center 10 years ago where they also reported a peak in that age bracket.[33] Male preponderance with a male-to-female ratio of 1.8:1 is also similar to the previous study in our center.[33] This finding was also reported by Efobi *et al*.[34] (1.2:1) and Hassan *et al*.[35] (2:1) in other parts of the country.

Among the patients seen in this study, 38 (59.4%) came on referral for specialized vitreoretinal care from other parts of the country, which may have been responsible for the increased awareness of their sickle cell status. The remaining patients who were unaware of their genotype at presentation may have been unaware of the ocular complications of SCD. Some studies[11,12,36] have reported increased awareness of SCD among their study population, but their knowledge of its symptoms and management was poor.[11,12] This reiterates the need for the establishment of multi-specialist genetic centers where carrier detection tests and genetic counseling facilities can be accessed as recommended by the World Health Organization.[37,38] Therefore, it would be important to collaborate with the hematologists, family physicians, and other stakeholders to educate everyone on the need to know their genotypes, ocular complications of SCD, and the need for a regular eye check-up and compliance with medical advice.

Genotype of the patients seen included Hb SC (94%), Hb SS (5%), and Hb CC (1%). This pattern is akin to an earlier study in our center.[33] Furthermore, this supports other findings[14-17,30] that ocular complications are more common in Hb SC patients due to its hypoxic effect on the retina and its accompanying sequela. In addition to revealing that ocular complications affect those with Hb SC more, Babalola and Wambebe[16] and Gill *et al*.[17] also recommended full ophthalmic screening of SCD patients at around the age of 10 years. This could be achieved with collaboration between the parents/guardians, pediatrician, ophthalmologist, and school authorities for mandatory Hb genotype screening. Afterward, those with SCD would be advised on the possibilities of developing ocular complications later in life, along with the utmost need for periodic eye checks to avert presenting at advanced stages and needless blindness.

In our study, about 53% and 45.3% of our patients presented with a BCVA of better than 6/18 in the right and left eyes, respectively. Conversely, more than one-third presented blind, i.e., BCVA worse than 3/60 (right eye – 39.1% and left eye –35.9%). A major reason for patients presenting to our clinic with BCVA worse than 3/60 could be the fact that more than half of the patients resided in other states of the country, and were referred to our hospital for specialized eye care. Other possible reasons include the late involvement of the macula and optic discs as stated by Al Alryalat *et al*.[39] and lack of needed personnel and equipment to manage the disease as reported by Babalola and Wambebe.[40]

More than four-fifths (86%) of our patients had proliferative sickle cell retinopathy with different stages of proliferation at presentation. Among them, 46 patients had PSR of Stage 3 and above. This could be due to the fact that our center provides tertiary health-care services, thus the referral pattern of advanced cases.

Retinal laser photocoagulation was mostly used for our patients, with more than half of patients receiving it as their first line of treatment and/or subsequent treatment. Its advantages include regression/prevention of new vessel formation and prevention of retinal detachment by sealing tractional retinal breaks/tears.[22,41] Despite the usefulness of the laser treatment, access of patients to this treatment is low, thus denying potential patients access to it. It is also important to note that the need to offer laser treatment to patients could exceed one session as the ocular disease keeps evolving. Therefore, all eye centers must be equipped with a laser photocoagulation machine, as this will go a long way in managing patients with PSR.

Intravitreal anti-VEGF was offered in cases of vitreous hemorrhage without findings of significant fibrovascular proliferation or tractional retinal detachment on ultrasound scan. A major benefit of anti-VEGF over laser photocoagulation is its lower risk of causing iatrogenic retinal tears and retinal detachment as reported by a previous study.[42]

Vitrectomy with or without anti-VEGF was offered for non-clearing vitreous hemorrhage. It is relatively expensive to set up, thus making it available in only a few centers. This limitation makes the procedure unaffordable and creates a backlog of patients needing the procedure. Scleral buckle was offered to some patients who presented with combined mechanism retinal detachment, with improved visual acuity. Prospects for optimal visual recovery may be unrealistic in our environment due to the dearth of skilled personnel and equipment as initially described by Yorston.[43] This results in progressive irreversible damage to the retina owing to the chronic nature of the disease. Amissah-Arthur and Mensah[31] reported some of the various hurdles SCD patients seeking health care in sub-Saharan Africa encounter. These include lack of comprehensive screening programs, limited access to specialized eye care services, resource constraints, and a paucity of consistent data. These include lack of comprehensive

screening programs, limited access to specialized eye care services, resource constraints, and paucity of consistent data.

Some of the limitations observed are the retrospective nature of this study and the inability to follow up the patients on a long term to monitor their visual acuity. Other limitations noted in the study were the inability of patients to afford some investigations like fundus fluorescein angiography and definitive treatment like vitrectomy.

Conclusion

This study has shown that proliferative sickle cell retinopathy, initially symptomless, is a sight-threatening disease. Furthermore, despite high genotype awareness among our patients, majority of our patients had at least Stage 3 proliferative sickle cell retinopathy at presentation, thus requiring multiple sessions of specialized vitreoretinal care. Therefore, it is essential for health-care providers and other stakeholders to design policies for improved genotype awareness and sustainable eye care programs for prompt recognition and treatment of SCD patients with sight-threatening lesions. Furthermore, the National Health Insurance Scheme should be strengthened and given wider coverage so that health care will be made accessible and affordable to this population.

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Conflicts of interest

There are no conflicts of interest.

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