Sickle Cell Retinopathy: Characterization among Patients Younger than 10 Years of Age

Aline Guerreiro Aguiar*, Levy Paz Aguiar, Verônica Larissa Vasconcelos Dos Santos, Larissa Estevam Sampaio and Dayse Cury De Almeida Oliveira

Department of Ophthalmology, Humberto Castro Lima Hospital (IBOPC), Salvador, Bahia, Brazil

*Corresponding Author: Aline Guerreiro Aguiar, Department of Ophthalmology, Humberto Castro Lima Hospital (IBOPC), Salvador, Bahia, Brazil.

Abstract

Purpose: This article aims to describe the prevalence of retinal alterations on the indirect binocular ophthalmoscopy exam in patients with SS and SC Sickle disease who are younger than 10 years of age in the city of Salvador in Brazil.

Methods: This is a retrospective study in which patients with sickle cell disease with an age group of 10 years or younger were attended in a service of retina in Salvador, Brazil in the last 10 years. All patients were submitted to the clinical file filling, which includes the sociodemographic profile, clinical profile and ophthalmologic examination. The patients were divided into two groups (SS or SC), according to the genotypic profile of hemoglobinopathy. The classification of retinopathy was performed according to Goldberg in proliferative and non-proliferative retinopathy. A P-value < 0.05 was considered statistically significant.

Results: A total of 90 patients (180 eyes) were evaluated, which 65 (72%) had SS sickle cell anemia and 25 (28%) had SC sickle disease. Of the 90 patients, 56 (62%) did not present retinal changes and 34 (38%) present sickle retinopathy. Of the 34 patients with retinopathy, 12 (35%) had non-proliferative sickle retinopathy and 22 (65%) had proliferative alterations. The increase in vascular tortuosity was the most observed non-proliferative sign (15,5% of eyes). It was observed that the two groups presented a similar proportion of areas of retinal non-perfusion (p = 1).

Conclusion: The results suggest the need for regular ophthalmologic follow-up of patients with sickle cell disease, even younger than 10 years of age, since in this study findings of non-proliferative sickle retinopathy were found in patients from 1 year of age and proliferative disease from 5 years.

*Keywords: Sickle Cell Anemia; Hemoglobin SC Disease; Retina; Retinal Diseases; Epidemiology*

Introduction

Hemoglobinopathies are a group of genetic diseases, characterized by the abnormal formation of the hemoglobin molecule (Hb). The alterations can be quantitative, where the reduction or absence in the globin chain synthesis occurs, being called thalassemias, or qualitative when there is alteration in the structure of these chains. In this group are the hemoglobinopathies S, in which the hemoglobin polymerizes in a shape that can lead to a hypoxia condition, modifying the form of erythrocytes assuming the characteristic sickled shape. The process of sickling results in a range of clinical manifestations, whose common denominators are hemolytic anemia and vaso-occlusive phenomena [1].

Among hemoglobinopathies S, we have homozygous individuals (SS) or carriers of double heterozygosis, such as SC individuals. Hemoglobin S is the most frequent Hb variant in Brazil, with sickle cell disease being one of the most prevalent hereditary diseases in the world, especially in African countries. On the other hand, hemoglobin C is the second most frequent Hb variant in Brazil and the world [1]. In the city of Salvador, Bahia, there is a population of about 80% of afro-descendants and frequencies of hemoglobin S is around 6.5 and 14.9% [2].

Sickle cell disease may manifest clinically in various organs, including the eye, by vaso-occlusive phenomena. Eye changes can occur in any ocular structure. The most common ocular complication in these hemoglobinopathies is retinopathy and there may be extensive areas of vascular occlusion with progressive loss of peripheral vascularization. This retinopathy results from the stasis and occlusion of small retinal vessels in its periphery. Among the forms of sickle cell disease, SS patients present a more severe systemic clinical form than those with SC hemoglobinopathy. On the other hand, ocular occlusive effects are more predominant and severe in type SC [3].

Retinopathy can be classified into proliferative and non-proliferative, according to Goldberg [4]. The most common non-proliferative lesions are the increase in vascular tortuosity, black sunburst and retinal hemorrhage like salmon patches. The stages of proliferative disease correlate chronologically with the appearance of proliferative changes, from the appearance of peripheral arteriolar occlusions (Figure 1) to retinal detachment [5].
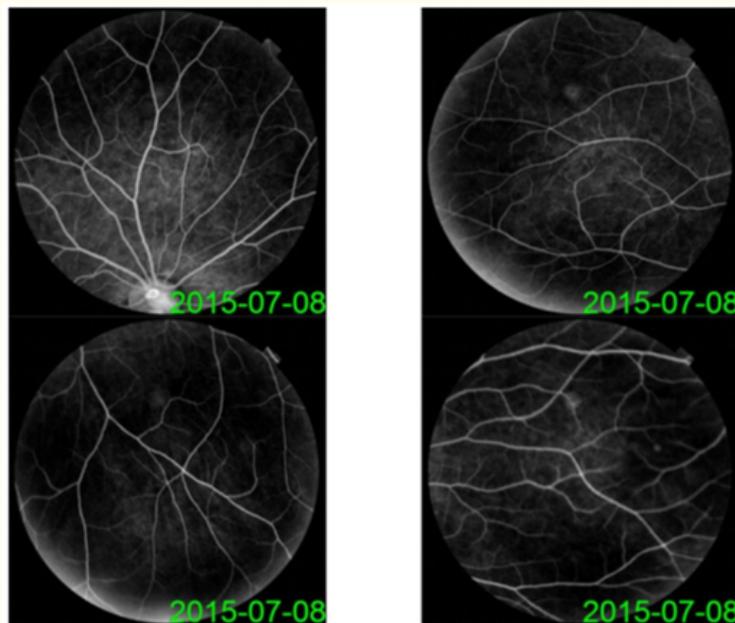
The retinal damage caused by sickle cell disease, whether SS or SC, although often self-limiting, tends to worsen over the years. Proliferative sickle cell retinopathy is observed at higher ages, especially over 20 years [6]. A consensus report of 2014 stated that annual or biannual screening for retinopathy is recommended from 10 years of age; however, the evidence for this recommendation was evaluated as being of low-quality [3].

Aim of the Study

This article aims to describe the prevalence of alterations on the indirect binocular ophthalmoscopy exam in patients with SS and SC Sickle disease who are 10 years of age or younger in a specialized service in the city of Salvador in Brazil.

Methods

This is a retrospective study in which patients with sickle cell disease with an age group of 10 years or younger were attended in the retina service of the Instituto Brasileiro de Oftalmologia e Prevenção da Cegueira (IBOPC), in the state of Bahia, Brazil from September 2008 to August 2018.

All patients were submitted to the clinical file filling during their consultation at the specialized service of retina of IBOPC, which includes the sociodemographic profile, clinical profile of sickle cell disease, genotypic profile of hemoglobinopathy (SS or SC pattern) and ophthalmologic examination.

In the ophthalmologic examination were performed:

1. Measurement of visual acuity with the best optical correction with Snellen table;

2. External ocular examination;

3. Fundus biomicroscopy;

4. Indirect binocular ophthalmoscopy.

Patients were divided into two groups according to their hemoglobinopathy pattern, SS group and SC group.

The classification of retinopathy was performed according to the one proposed by Goldberg in 1971 in proliferative and non-proliferative retinopathy, as well as proliferative retinopathy was classified in 5 stages of Goldberg: stage I characterized by the presence of peripheral arteriolar occlusions; stage II by peripheral arteriovenous anastomoses; stage III by neovascular proliferation or fibrosis; stage IV by vitreous hemorrhage and stage V by retinal detachment [4]. The findings of retinal non-proliferative disease were increased vascular tortuosity, black sunburst, salmon patches, angioid streaks and iridescent spots [4]. When the patient presented eyes with different classification, it was considered the worst severity to characterize their retinopathy.

Statistical analysis was performed using EpiInfo 7.1 for Windows. Qualitative variables were described using simple and relative frequency tables. For comparisons between the groups, for the events of interest, chi-square, Bartlett's Test or Fisher exact tests were used. A P-value < 0.05 was considered statistically significant.

Results

A total of 90 patients (180 eyes) were evaluated, which 65 (72%) had SS sickle cell anemia and 25 (28%) had SC sickle disease. Of these 90 patients, 50 (55,5%) were female and 40 (44,5%) were male. The mean age was 7.65 ± 2.03 years, with a minimum of 1 and a maximum of 10 years. Between the SS and SC groups, there was no statistically significant difference concerning the age group, but to the gender, there was a higher proportion of female patients in the SC group, as shown in table 1.

The best-corrected visual acuity in 163 (90,5%) eyes was 20/20 or 20/25, it was considered normal vision. No significant statistical difference was observed between visual acuity among patients in the SS and SC groups (p = 0,085). When comparing the prevalence of normal vision among patients in the study with sickle cell retinopathy and the patients without signs of sickle cell retinopathy, no statistically significant difference was observed (p = 0,790).

	Hemoglobin SS (n = 53)	Hemoglobin SC (n = 44)	Total (n = 97)	p-value
Gender				
Male	34 (52%)	6 (24%)	40 (44,5%)	0,018*
Female	31 (48%)	19 (76%)	50 (55,5%)	
Age, years				
Mean + SD	7,72 ± 1,87	7,48 ± 2,43	-	0,112**
Range	1 - 10	1 - 10	-	

***Table 1:** Demographic characteristics of patients.*
*SD: Standart Deviation; *: Fisher Exact Test; **: Bartlett's Test.*

Of the 90 patients, 56 (62%) did not present retinal changes and 34 (38%) present sickle retinopathy. Of the 34 patients with retinopathy, 12 (35%) had non-proliferative sickle retinopathy and 22 (65%) had proliferative alterations.

We have a higher prevalence of sickle cell retinopathy in patients of the group SS, in which 40% of these patients had some sign of retinopathy, while 24% of SC patients had the same outcome, but there was no statistical significance (p = 0.055). There was an increase in the prevalence of sickle cell retinopathy in patients with more age, with a prevalence of 21% in the 1 - 5 age group and 38% in the 6 - 10 age group, however, there was no statistical significance (p = 0.131). Table 2 shows the distribution of the type of sickle cell retinopathy (proliferative or non-proliferative) according to the patient's age range and the hemoglobinopathy pattern.

Age (years)	Ocular lesions	Hemoglobin SS (n = 65)	Hemoglobin SC (n = 25)	Total (n = 90)	p-value*
1 - 5	Normal	5 (62,5%)	6 (100%)	11 (78,5%)	N/A
	Non-proliferative lesions	3 (37,5%)	0 (0%)	3 (21,5%)	
	Proliferative lesions	0 (0%)	0 (0%)	0 (0%)	
6 - 10	Normal	33 (58%)	12 (63%)	45 (59%)	0,590
	Non-proliferative lesions	8 (14%)	1 (5%)	9 (12%)	
	Proliferative lesions	16 (28%)	6 (32%)	22 (29%)	

***Table 2:** The distribution of ocular lesions based on the Goldberg classification for sickle cell retinopathy*
in the hemoglobin SS and hemoglobin SC groups, stratified by age group.
* Chi-Square Test.

The increase in vascular tortuosity was the most observed non-proliferative sign (23% of eyes), with a higher prevalence in the SS group (p = 0.00005). Regarding proliferative disease findings, it was observed that the two groups presented a similar proportion of findings of areas of retinal nonperfusion (p = 1.00), shunts arteriovenous (p = 0.074) and areas of neovascularization (p = 0.277). Table 3 shows the observed frequency of retinal changes in the SS and SC groups.

None of the patients in the study had previous treatment for complications resulting from sickle cell retinopathy, such as laser photo-coagulation or posterior vitrectomy. Regarding the clinical treatment of sickle cell disease, all patients were taking regular folic acid, while the use of hydroxyurea was observed more frequently in the SS group (p = 0.009).

	Hemoglobin SS (n = 130)		Hemoglobin SC (n = 50)		Total (n = 180)		p-value*
	n	%	n	%	n	%	
Vascular tortuosity	28	21,5	0	0	28	15,5	0,00005
Salmon patches	2	1,5	2	4	4	2,2	0,308
Black sunburst	1	0,8	3	6	4	2,2	0,065
Iridescent spots	5	3,8	2	4	7	4	1
Angioid streaks	0	0	0	0	0	0	1
Peripheral arteriolar occlusions	30	23	11	22	41	23	1
Shunts arteriovenous	5	3,8	6	12	11	6	0,074
Neovascular proliferation	0	0	1	2	1	0,5	0,277
Vitreous hemorrhage	0	0	0	0	0	0	1
Retinal detachment	0	0	0	0	0	0	1

Table 3: *Fundoscopic ocular lesions in both sickle cell disease groups.*

*: Fisher Exact Test.

Discussion

In this study, we observed that 38% of patients 10 years of age or younger presented some signs of sickle cell retinopathy at ocular examination, presenting statistically similar rates in both SS and SC groups. However, the visual acuity of the patients with retinal disease was little affected, being similar to the patients without retinal alterations, as observed in previous studies [4,6-11].

There was a proportional increase in the presence of signs of sickle cell retinopathy with increasing age, but it was not statistically significant (p = 0.234). In previous studies, there is a correlation between the increase in the prevalence of sickle cell retinopathy with increasing age [6,12-14].

Findings of non-proliferative retinopathy as increased vascular tortuosity and black sunbursts are the most commonly observed in other studies [6,8-10,15,16]. In this study, the most common non-proliferative alterations were increased vascular tortuosity and iridescent spots, followed by black sunbursts and salmon patches, and with respect to the first alteration there was statistical difference between the groups, with more prevalence in SS group (p = 0,00005), but related to the others alterations there was no statistical difference.

It is expected that proliferative retinopathy is observed more frequently in SC patients [3,12,15,16]. Notwithstanding, the findings of proliferative retinopathy were observed in equal proportion in both groups, and only in patients over 5 years of age. However, a high prevalence of proliferative retinopathy was observed compared to previous studies, being present in 35 (26,9%) SS patients and 18 (36%) SC [3,11,15].

Limitations of the Study

Despite the limitations of this study, such as small numbers of patients, retrospective analysis and absence of randomization, the results suggest the need for regular ophthalmologic follow-up of patients with sickle cell disease, even younger than 10 years of age, since in this study findings of non-proliferative sickle retinopathy were found in patients from 1 year of age and proliferative disease from 5 years.

Conclusion

The results suggest the need for regular ophthalmologic follow-up of patients with sickle cell disease, even younger than 10 years of age, since in this study findings of non-proliferative sickle retinopathy were found in patients from 1 year of age and proliferative disease from 5 years.

Disclosure

None of the authors have any financial/conflicting interests to disclose.

Ethical Approval

Approved by the following research ethics committee: CPqGM/FIOCRUZ 165/2008.

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