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Sickle cell retinopathy: characterization among patients over 40 years of age

Retinopatia falcêmica: caracterização da doença na população acima de 40 anos de idade

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ABSTRACT

Purpose: *This article aims to describe the prevalence of retinal alterations on the indirect binocular ophthalmoscopy exam in patients with sickle cell disease (HbSS or HbSC) who are over 40 years of age.* ***Methods:*** *This is a retrospective study in which patients with sickle cell disease (SCD) with an age group of 40 years or older were attended in a service of retina in Salvador, Brasil on 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 in two groups (SS or SC), according to genotypic profile of hemoglobinopathy (HbSS or HbSC). 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 97 patients (194 eyes) were evaluated, being 44 (45%) of the SC group and 53 (55%) of the SS group. Of the 97 patients, 19 (19.5%) did not present retinal changes and 78 (80,5%) present sickle cell retinopathy. Of the 78 patients with retinopathy, 22 (28%) had nonproliferative sickle retinopathy and 56 (72%) had proliferative alterations. The increase in vascular tortuosity was the most observed nonproliferative sign (26.8% of eyes) in both groups. The SC patients presented a greater proportion of findings of areas of retinal non perfusion (30%) than SS patients (p = 0.015).* ***Conclusion:*** *The results suggest the need for regular ophthalmologic follow-up of patients with SCD, especially in the older age group, due to the high prevalence of 80.5% of findings of sickle cell retinopathy on examination in patients over 40 years old.*

Keywords: *Sickle cell anemia; Hemoglobin C disease; Retina; Retinal diseases; Epidemiology*

RESUMO

Objetivos: Este artigo tem como objetivo avaliar a prevalência de alterações retinianas observadas pelo exame de oftalmoscopia binocular indireta em pacientes com doença falciforme (HbSS e HbSC) com mais de 40 anos de idade. **Métodos:** Estudo retrospectivo com pacientes com doença falciforme (DF) na faixa etária acima de 40 anos, atendidos em serviço especializado em Salvador, Brasil nos últimos 10 anos. Todos os pacientes foram submetidos ao preenchimento da ficha clínica, em que incluía perfil sociodemográfico, clínico e exame oftalmológico. Os pacientes foram divididos em dois grupos (SS ou SC), de acordo com seu padrão genotípico da hemoglobinopatia (HbSS ou HbSC). A classificação da retinopatia foi realizada de acordo com Goldberg em retinopatia não proliferativa e proliferativa. Um valor de p<0.05 foi considerado estatisticamente significante. **Resultados:** Um total de 97 pacientes (194 olhos) foram avaliados, sendo 44 (45%) do grupo SC e 53 (55%) do grupo SS. Dos 97 pacientes, 19 (19,5%) não apresentavam alterações retinianas e 78 (80,5%) apresentavam retinopatia falcêmica. Destes 78 pacientes com alterações retinianas, 22 (28%) possuem sinais de retinopatia não proliferativa e 56 (72%) possuem alterações proliferativas. O aumento da tortuosidade vascular foi o sinal de doença não proliferativa mais observado (26,8% dos olhos) em ambos os grupos. Os pacientes do grupo SC apresentaram a maior proporção de achados proliferativos, como áreas de não perfusão retiniana, que os pacientes SS (30%) (p = 0.015). **Conclusão:** Os resultados sugerem a necessidade de manter um acompanhamento oftalmológico regular dos pacientes com DF, especialmente pacientes com maior faixa etária, devido à alta prevalência observada (80,5%) de retinopatia falcêmica em pacientes acima de 40 anos de idade.

Descritores: Anemia falciforme; Doença da hemoglobina C; Retina; Doenças retinianas; Epidemiologia

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Introduction

Hemoglobinopathies are a group of genetic diseases, characterized by the abnormal formation of the hemoglobin molecule (Hb).[1] The alterations can be quantitative, where the reduction or absence in the globin chain synthesis occurs, being called thalassemias, or qualitative when there is an 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.[1] 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, are homozygous individuals (HbSS) or carriers of double heterozygoses, such as HbSC individuals. Hemoglobin S is the most frequent Hb variant in Brazil, with sickle cell disease (SCD) being one of the most prevalent hereditary diseases in the world, especially in African countries.[2] 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]

SCD may manifest clinically in various organs, including the eye, by vaso-occlusive phenomena.[3] Eye changes can occur in any ocular structure.[4] 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.[4] This retinopathy results from the stasis and occlusion of small retinal vessels in its periphery.[3] Among the forms of SCD, SS patients present a more severe systemic clinical form than those with SC hemoglobinopathy.[3] 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.[5] The stages of proliferative disease correlate chronologically with the appearance of proliferative changes, from the appearance of peripheral arteriolar occlusions to retinal detachment.[5]

The retinal damage caused by SCD, whether SS or SC, although often self-limiting, tends to worsen over the years.[3] A consensus report stated that annual or biannual screening for retinopathy is recommended from 10 years of age, but the evidence for this recommendation was evaluated as being of low-quality.[3] Proliferative sickle cell retinopathy is observed at higher ages, especially over 20 years.[6] This article aims to describe the prevalence of alterations on the indirect binocular ophthalmoscopy exam in patients with SS and SC sickle cell disease who are over 40 years of age in a specialized service in the city of Salvador in Brazil, since there are few studies on the prevalence of retinopathy in older age groups.

Methods

This is a retrospective study in which patients with SCD with an age group of 40 years or older were attended in the retina service of the Instituto Brasileiro de Oftalmologia e Prevenção da Cegueira (IBOPC), in the state of Bahia, Brazil from August 2008 to September 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 or Bartlett's tests were used. A P-value <0.05 was considered statistically significant.

Results

A total of 97 patients (194 eyes) were evaluated, of which 44 (45%) had SC sickle cell disease and 53 (55%) had SS. Of these 97 patients, 68 (70%) were female and 29 (30%) were male. The mean age was 48.97 ± 7.34 years, with a minimum of 40 and a maximum of 70 years. Between the two SS and SC groups, there was no statistically significant difference concerning the demographic data, as shown in table 1.

The best-corrected visual acuity in 124 (64%) 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 ($p = 0.202$). It was observed that in more advanced stages of retinopathy the number of patients with vision worse than 20/25 was increasing, being 23.5% in stage I, 35% in II, 34% in III, 75% in IV and 86% in V ($p = 0.013$). 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 ($p = 0.547$).

Of the 97 patients, 19 (19.5%) did not present retinal changes and 78 (80,5%) present signs of sickle cell retinopathy. Of the 78 patients with retinopathy, 22 (28%) had non-proliferative retinopathy and 56 (72%) had proliferative alterations.

Although there was an increase in the prevalence of sickle cell retinopathy in patients with more advanced age, with a prevalence of 78% in the 40-49 age group, 83% in the 50-59 age group and 89% in the group with 60 or more years of age, there was no statistical significance ($p = 0.692$). Table 2 shows the dis-

Table 1
Demographic characteristics of patients

	Hemoglobin SS (n=53)	Hemoglobin SC (n=44)	Total (n=97)	p-value
Gender				
Male	17 (32%)	12 (27.3%)	29 (29.9%)	0.606*
Female	36 (68%)	32 (72.7%)	68 (70.1%)	
Age, years				
Mean + SD	49.2 ± 7.3	48.6 ± 7.3	-	0.975**
Range	40-65	40-70	-	

SD= Standart deviation;*Chi-squared; **Bartlett's Test.

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

Age (years)	Ocular lesions	Hemoglobin SS (n=53)	Hemoglobin SC (n=44)	Total (n=97)	p-value*
40-49	Normal	6 (21,5%)	7 (22,6%)	13 (22,0%)	0,7
	Non-proliferative lesions	8 (28,5%)	6 (19,4%)	14 (23,7%)	
	Proliferative lesions	14 (50,0%)	18 (58,0%)	32 (54,3%)	
50-59	Normal	5 (25%)	0	5 (17,25%)	0,0323
	Non-proliferative lesions	5 (25%)	0	5 (17,25%)	
	Proliferative lesions	10 (50%)	9 (100%)	19 (65,5%)	
≥60	Normal	1 (20%)	0	1 (11,1%)	0,4868
	Non-proliferative lesions	1 (20%)	2 (50%)	3 (33,3%)	
	Proliferative lesions	3 (60%)	2 (50%)	5 (55,6%)	

* Chi-square test

Table 3
Fundoscopic ocular lesions in both sickle cell disease groups

	Hemoglobin SS (n=106)		Hemoglobin SC (n=88)		Total (n=194)		p-value*
	n	%	n	%	n	%	
Vascular tortuosity	33	31,1	19	21,6	52	26,8	0,135
Salmon patches	0	0	2	2,2	2	1	0,118
Black sunburst	15	14,1	12	13,6	27	13,9	0,917
Iridescent spots	0	0	0	0	0	0	1
Angioid streaks	2	1,9	0	0	2	1	0,195
Peripheral arteriolar occlusions	17	16	27	30,7	44	22,7	0,015
Shunts arteriovenous	10	20	20	37,7	30	29,1	0,047
Neovascular proliferation	12	11,3	23	26,1	35	18	0,007
Vitreous hemorrhage	2	1,9	2	2,2	4	2	0,85
Retinal detachment	2	1,9	4	4,5	6	3	0,286

* Chi-square

tribution of the type of sickle cell retinopathy (proliferative or non-proliferative) according to the patient's age range and the hemoglobinopathy pattern.

The increase in vascular tortuosity (Figure1) was the most observed non-proliferative sign (26.8% of eyes) in both groups, without a significant statistical difference (p=0.135). Regarding proliferative disease findings, it was observed that SC patients presented a greater proportion of findings of areas of retinal non-perfusion (p=0.015), shunts arteriovenous (p=0.047) and areas of neovascularization (p = 0.007) than SS patients. Table 3 shows the observed frequency of retinal changes in the SS and SC groups.

The prevalence of previously treated for ocular complications resulting from sickle cell retinopathy with laser photocoagulation or posterior vitrectomy was higher in the SC group, in which 34% had previous ocular treatment and only 7% of SS patients had the same outcome (p = 0.014).

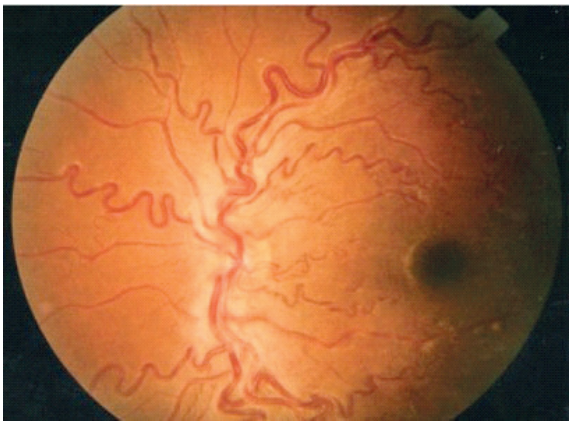

Figure 1: Increase in vascular tortuosity

Discussion

In this study, we observed that 80.5% of patients over 40 years of age presented some signs of sickle cell retinopathy at the 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, 6-10]

There was a proportional increase in the presence of signs of sickle cell retinopathy with increasing age, but it was not statistically significant (p = 0.692). In previous studies, there is a correlation between the increase in the prevalence of sickle cell retinopathy with increasing age. [6,11,12]

Findings of non-proliferative retinopathy as increased vascular tortuosity and black sunbursts are the most commonly observed in other studies.[6, 8-10, 13, 14] As in this study, these non-proliferative alterations were the most common, and there was no statistical difference between the two SS and SC groups (p = 0.135 and p = 0.917, respectively).

The findings of proliferative disease were observed in a greater proportion in patients of the SC group. This is expected according to previous studies in which proliferative retinopathy are observed more frequently in SC patients.[3, 11, 13, 15] The pathophysiology associated with this phenomenon is still unknown, and the present study lacks data to elucidate this fact. It is hypothesized that SS disease may have a protective effect against ocular vaso-occlusive events due to reduced blood viscosity.[15]

Besides, a set of factors such as mean corpuscular volume, increased blood viscosity and density, as well as the decreased level of fetal hemoglobina, seem to explain the high prevalence of retinopathy in SC sickle cell disease in relation to SS.[13]

Despite the limitations of the study, such as small numbers of patients, retrospective analysis and absence of randomization, the results of this study suggest the need for regular ophthalmologic follow-up of patients with SCD, especially in the older age group, due to the high prevalence of 80.5% of findings of sickle cell retinopathy on examination in patients over 40 years old.

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