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### Scientific comment

## An eye on sickle cell retinopathy<sup>☆</sup>



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Sickle cell disease (SCD) is caused by a single point mutation at the sixth position in the  $\beta$ -globin chain that substitutes the amino acid valine for glutamic acid resulting in sickle hemoglobin (Hb S). Despite being characterized by the same point mutation, the clinical course of SCD is extremely variable, ranging from mild to very severe depending on the different genotypes.<sup>1–4</sup> Patients with sickle cell anemia (SCA), the most common and most severe form of SCD, have two copies of the altered gene, a genotype referred to as Hb SS. Hemoglobin C (Hb C) occurs frequently in compound heterozygosity with Hb S with the resulting SC disease (Hb SC) being relatively more benign than homozygous Hb SS. However, for reasons not well understood, these patients are more likely to be affected by thromboembolic complications, renal papillary necrosis and retinopathy.<sup>5,6</sup>

Both the anterior and posterior segments of the eye can be compromised due to the pathological processes of SCD but ocular manifestations in the retina are considered the most important in terms of frequency and visual impairment.<sup>7</sup> Sickle cell retinopathy develops in up to 42% of individuals during the second decade of life.<sup>8</sup> It is triggered by vaso-occlusion of the ocular microvasculature, as opposed to diabetic retinopathy which is associated with overexposure of

the vascular tissues to hyperglycemia, and may lead to visual impairment depending on its localization and affected tissue. Sickle cell retinopathy can be classified as non-proliferative or proliferative. In the non-proliferative form the most common clinical findings are salmon patch hemorrhages, iridescent spots and black sunbursts, which can be observed in the peripheral retina. Moreover, venous tortuosity, enlargement of the foveal avascular zone, central retinal artery obstruction and peri-papillary and peri-macular arteriolar occlusions have been reported in the central part of the retina. Angioid streaks can be observed in association with sickle cell-thalassemia disease, SCA and SCD.<sup>9,10</sup>

Proliferative sickle cell retinopathy (PSCR) complications are a major contributor to vision loss, leading to visual impairment in 10–20% of affected eyes. There is a low frequency of visual loss in SCD which may be explained, at least in part, by the high frequency of spontaneous regression (20–60% of cases) through the development of atrophic lesions or autoinfarction. Spontaneous regression, which occurs most frequently about 2 years after the development of PSCR, is an important determinant in the natural history of PSCR.<sup>11–13</sup> The highest prevalence of PSCR in SCA patients occurs between 25 and 39 years of age in both men and women. However, in SCD

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<sup>☆</sup> See paper by Oliveira DCA et al. on pages 340–4.

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patients it occurs earlier: between 15 and 24 years in men and from 20 to 39 years in women.<sup>13</sup> Peripheral retinal neovascularization develops after vaso-occlusion of the peripheral retina and grows anteriorly from perfused to non-perfused retina.<sup>14</sup> Initially these new vessels are flat and denominated sea fan for their close resemblance to the marine invertebrate *Gorgonia flabellum*. Neovascularization in sea fans, even small sea fans, is capable of causing vitreous hemorrhage. This complication happens due to the constant leaking of blood components into the vitreous through the fragile neovascular tissue. The repetition of this hemorrhagic phenomenon leads to worsening of the vitreo-retinal traction, with the potential of causing rhegmatogenous or tractional retinal detachment.<sup>12,15</sup>

It is important to note that there is an inverse relationship between the severity of systemic disease and the severity of retinopathy in homozygous SS individuals compared to compound heterozygous SC subjects. Sickle cell patients have more systemic complications with multiple vaso-occlusive events and secondary organ damage. Heterozygous patients, on the other hand, have fewer systemic complications, but an increased frequency and early onset retinal neovascularization. According to a longitudinal study developed over 20 years in Jamaica, the prevalence of PSCR was greater in SCD patients. The authors reported that PSCR had developed by the age of 24 years in 43% and 14% of subjects with Hb SC disease and SCA, respectively.<sup>12</sup> The high prevalence of retinopathy observed in Hb SC patients may be the consequence of this more benign genotype. The postulated mechanism of action is that an enhanced circulatory competence of Hb SC cells would preserve the retinal circulation allowing posterior development of proliferative lesions.<sup>16</sup> On the other hand, in SCA patients there is an early and a more complete occlusion of peripheral retinal vessels and hence further retinal vascular damage and proliferative lesions are rare. This phenomenon may explain why a benign genotype such as SC disease presents a higher frequency of PSCR compared with the SS genotype. One possible explanation proposed by Fabri and Kaul is based on three models with different vaso-occlusive tendencies. These models are based on low, intermediate and high vaso-occlusive indices, with SC disease being represented by the intermediate model, that is, with vaso-occlusion sufficient to produce retinal ischemia, but insufficient to occlude the developing PSCR lesions.<sup>13,17</sup>

The article entitled "Sickle cell disease retinopathy: characterization among pediatric and teenage patients from northeastern Brazil" by Oliveira et al. and published in this edition of the Revista Brasileira de Hematologia e Hemoterapia describes a population of SCD patients from the state of Bahia, according to their ophthalmologic characteristics.<sup>18</sup> The main point of the study is the confirmation that retinal changes have early onset in both SCA and SC disease patients. Their findings corroborate previous reports in different populations and confirm the need for ophthalmological monitoring of patients from early childhood in order to avoid visual impairment as PSCR is usually asymptomatic until complications such as vitreous hemorrhage or retinal detachment occur.

In addition to the eye examination, it is important to note the presence of factors that increase the chance of developing SCPR as has been reported by other research groups. In SCD

patients, pain crisis, male gender and splenic sequestration suggest the need for earlier ophthalmic screening. Characteristics of PSCR, such as neovascular and fibrous proliferations (sea fan), vitreous hemorrhage and retinal detachment, are associated with older age, pulmonary disease, deafness or tinnitus and no history of osteomyelitis in patients with SC disease. In SCA patients, older age, male gender and history of acute pyelonephritis were associated with the development of PSCR.<sup>19-21</sup> Regarding laboratory findings, high total hemoglobin in males and low fetal hemoglobin in both males and females were observed in SCA patients. In SCD patients, increased mean cell volume and low fetal hemoglobin were reported in both genders and high total hemoglobin and high mean corpuscular hemoglobin concentration were observed in men.<sup>7,13,14,22</sup>

## Conflicts of interest

The author declares no conflicts of interest.

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