Review Article

Sickle Cell Retinopathy: a Review

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Abstract

Sickle cell disease is one of the most prevalent hemoglobinopathies in the world. In Iran, sickle cell disease is more common in southern parts of the country such as Khuzestan province. Retinopathy is the most representative ocular complication of sickle cell disease. Sickle cell retinopathy is characterized by the vaso-occlusion of capillary beds and is classified in two types of proliferative and non-proliferative according to presence or absence of vascular proliferation in fundus. In non-proliferative sickle cell retinopathy, the retinal changes do not involve neovascularization as they do in proliferative sickle cell retinopathy. The two most severe complication of proliferative sickle cell retinopathy are vitreous hemorrhage and retinal detachment, which may lead to visual loss. Identification and prompt referral of these patients has a critical role in prevention of irreversible visual loss. Newer imaging modalities such as ultra-wide field fluorescein angiography, spectral domain optical coherence tomography and optical coherence tomography angiography are now available. These techniques can detect the sickle cell retinopathy in its early stages.

In this review, we briefly discuss the manifestations, diagnosis and management of sickle cell retinopathy.

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Introduction

Sickle cell disease (SCD) is one of the most common hemoglobinopathies in the world with millions of people currently affected across the globe [1]. The prevalence of SCD in southern parts of Iran is high, especially in Khuzestan province [2].

Sickle cell anemia (SCA), which is the leading group within SCD, results from a point mutation (A-T) in the sixth codon of the b-globin gene resulting in the substitution of glutamic acid with valine at position 6 of the b globin chain forming hemoglobin sickle (Hb S) [3,4]. The homozygous Hb S genotype (ie, SS) represents a severe common form of SCD [5].

HbS has different properties compared to normal hemoglobin. It polymerizes when deoxygenated, leading to cellular alterations that changes the red cell shape into a rigid and sickled form [6]. The most important factor in the pathophysiology of SCD is vaso-occlusion, which leads to ischemia [7]. In addition, multiple other events including hemolysis associated reduction in nitric oxide bioavailability, chronic inflammation, oxidative stress, altered red cell adhesive properties, activated white blood cells and platelets and finally altered hemostasis play a critical role in pathogenesis of this disease [8].

Improved survival in SCD has led to higher manifestations of morbidities, which are becoming more apparent in older patients [9]. One of the organs affected in SCD are eyes [5,10]. Both the anterior and posterior segments of the eye can be affected, but ocular manifestations in the retina are the most important in terms of frequency and visual impairment [11]. The blood flow in terminal retinal arterioles may be decreased by the aggregation of rigid sickled cells [12]. Under these conditions, the available Hb is deoxygenated and cannot supply the oxygen demand [12].

In this manuscript, sickle cell retinopathy, its manifestations, diagnosis and management will be discussed.

Ophthalmic Manifestations of SCD

The pathological process of SCD can affect every vascular bed in the eye and in its advanced stage has the potential to cause visual loss [13]. Ocular complications of SCD result from occlusion of small eye vessels by sickled erythrocytes and may involve both anterior and posterior segments including orbit, iris, conjunctiva, uvea, and especially retina [11, 14]. Among possible ocular manifestations, the most representative is retinopathy, which can lead to blindness if left untreated [11]. Sickle cell retinopathy (SCR) develops in up to 42 % of patients with SCD during the second decade of life [11,15]. SCR is classified in two types: proliferative and non-proliferative, which is based on the presence or absence of vascular proliferations [5].

Non-proliferative sickle cell retinopathy (NPSCR)

NPSCR, is more commonly observed in SCA patients with SS genotype [5]. In this form of retinopathy, the retinal periphery of patients shows bilateral changes like salmon patch hemorrhages, iridescent spots, black sunbursts and angioid streaks [5,11]. The findings in the central part of retina include foveal avascular zone, arteriovenous tortuosity, and central retinal artery occlusion (CRAO), as well as peripapillary and perimacular arterial occlusion [5,11]. CRAO, which results in macular ischemia, is a rare but potentially devastating cause of blindness in patients with SCA with an unpredictable course but potential for visual recovery [16].

Proliferative sickle cell retinopathy (PSCR)

PSCR, which is more commonly observed in

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SCA patients with SC genotype, is caused by the high prevalence of abnormal peripheral retinal vasculature and causes some degree of visual loss in 5-20 % of patients [5]. Older age, male gender and history of acute pyelonephritis are some risk factors for development of PSCR among SCA patients [17-20].

Peripheral changes caused by PSCR generally include occlusions of the superficial and deep capillary plexus, which cause acute paracentral middle maculopathy, leading to thinning of macular inner retinal layers [5]. These peripheral retinal vascular occlusions cause tissue ischemia and release of angiogenic mediators that promote retinal neovascularization [5]. Then, this neovascularization grows anteriorly from the vascularized to avascular retina and shapes the hallmark sign in PSCR patients, which is called the "sea fan configuration" [5]. The sea fan configuration is a pre-retinal fibrovascular membrane involving primarily the retinal nerve fiber and ganglion cell layers [5]. Sea fan structures spontaneously regress in 20 %-60 % of patients through the development of atrophic lesions or auto-infarction, which can explain why most patients maintain good vision years after a PSCR event [5].

Staging

Goldberg [21] has classified the SCR into five stages based on its severity: Stage I is characterized by peripheral arterial occlusion due to decreased deformability of erythrocytes, stagnant flow, and thrombosis [5]. In stage II the peripheral arteriovenous anastomoses appear to compensate for hypoxia caused in the first stage [5]. In stage III, pre-retinal neovascularization occurs as a result of angiogenic factors from the peripheral ischemic retina, forming the retinal sea fans [5]. Stage IV is characterized by vitreous hemorrhage, which is the result of bleeding from the neovascularization in previous stage [22]. Finally, stage five is characterized by tractional retinal detachment, which might lead to visual loss [14].

Diagnosis

Diagnosis of SCR is based on typical clinical examinations in the presence of a history of SCD, including measurement of visual acuity and intraocular pressure, complete dilated fundoscopy, slit-lamp biomicroscopy, retinography, fluorescein angiography, spectral domain optical coherence tomography and optical coherence tomography angiography [5,14, 20, 22-28].

Treatment

Treatment for SCR remains palliative [5]. Chemotherapy (hydroxyurea ± anti- vascular endothelial growth factor), as well as phlebotomy in conjunction with long-term blood transfusions to reduce total content of HbS in red cells might be helpful in controlling the SCR [5]. Conventional local therapies for SCR include diathermy, cryotherapy and argon or xenon photocoagulation, as well as surgical treatment, which is indicated for complications of proliferative retinopathy, such as retinal detachment and vitreous hemorrhage [14, 29, 30].

Discussion

Ophthalmic manifestations of SCA including retinopathy are increasing with improved survival among patients in recent years [13]. General practitioners, paediatricians, haematologists and ophthalmologists should be aware of these ophthalmic manifestations to achieve on time diagnosis and treatment. It should be noted that the best approach for prevention of SCR is reducing the prevalence of SCA by controlling the spread of the HbS gene

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pool, which can be achieved by genetic counseling before marriage [5]. Since SCR among SCA patients results from a systemic pathological process causing anemia, prevention of SCR can be also achieved with better treatment of underlying anemia, using several approaches such as increase in fetal hemoglobin, erythrocyte hydration, use of anti-inflammatory drugs, antioxidant therapy, antithrombotic drugs, decreasing the HbS by transfusion and apheresis, as well as hematopoietic stem cell transplantation and gene therapy [14]. Hematopoietic stem cell transplantation has the potential to cure SCD and prevent retinopathy, but this treatment may cause complications including infertility, graft rejection and graft-versus-host disease causing a mortality rate of 5-10 % [17].

Most studies in different populations, confirm the importance of periodic eye exams among patients with SCA [5]. The development of SCR is highly unlikely among patients under 10 years old, thus serial biannual examinations has been suggested for patients with SCA older than 10 years to detect SCR in its early stages and to consider treatment before severe complications [18].

It should be noted that SCR, especially in its proliferative form, is more frequent and more severe among patients with SC genotype than those patients with SS genotype, which necessitates special attention to retinal changes among these patients [5,14].

Conclusion

Eye manifestations of SCA including retinopathy are increasing with improved survival among patients in recent years. Considering that sickle cell retinopathy is a complication that might cause blindness in affected patients, its on time diagnosis and treatment should be a goal for both hematologists and ophthalmologists caring for these patients. Some new diagnostic and treatment modalities have been suggested for patients with SCR in recent years. Whether these advances may lead to improved management and treatment outcomes remain unanswered. Further studies especially randomized clinical trials with sufficient sample size are needed to compare the usefulness of these new diagnostic and treatment modalities. Future advances in treatment of SCA itself might lead to reduction of ophthalmologic manifestations of this disease.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.

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