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REVIEW ARTICLE

Sickle cell retinopathy. A focused review

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Abstract

Purpose To provide a focused review of sickle cell retinopathy in the light of recent advances in the pathogenesis, multimodal retinal imaging, management of the condition, and migration trends, which may lead to increased prevalence of the condition in the Western world.

Methods Non-systematic focused literature review.

Results Sickle retinopathy results from aggregation of abnormal hemoglobin in the red blood cells in the retinal microcirculation, leading to reduced deformability of the red blood cells, stagnant blood flow in the retinal precapillary arterioles, thrombosis, and ischemia. This may be precipitated by hypoxia, acidosis, and hyperosmolarity. Sickle retinopathy may result in sight threatening complications, such as paracentral middle maculopathy or sequelae of proliferative retinopathy, such as vitreous hemorrhage and retinal detachment. New imaging modalities, such as wide-field imaging and optical coherence tomography angiography, have revealed the microstructural features of sickle retinopathy, enabling earlier diagnosis. The vascular growth factor ANGPTL-4 has recently been identified as a potential mediator of progression to proliferative retinopathy and may represent a possible therapeutic target. Laser therapy should be considered for proliferative retinopathy in order to prevent visual loss; however, the evidence is not very strong. With recent development of wide-field imaging, targeted laser to ischemic retina may prove to be beneficial. Exact control of intraoperative intraocular pressure, including valved trocar vitrectomy systems, may improve the outcomes of vitreoretinal surgery for complications, such as vitreous hemorrhage and retinal detachment. Stem cell transplantation and gene therapy are potentially curative treatments, which may prevent retinopathy.

Conclusions There is lack of evidence regarding the optimal management of sickle retinopathy. Further study is needed to determine if recent progress in the understanding of the pathophysiology and diagnosis of sickle retinopathy may translate into improved management and outcome.

Keywords Hemoglobin S · Hemoglobin C · Ischemia · Neovascularization · Panretinal photocoagulation · Sickle cell retinopathy

Introduction and epidemiology

Current geopolitical scenario and ongoing waves of immigration may lead to new challenges for practicing ophthalmologists, requiring an increased awareness to diagnose and ability to manage sickle cell disease (SCD) and sickle cell retinopathy. For example, in 2016, 863.3 thousand citizens of non-member countries residing in an EU Member State acquired EU citizenship (Eurostat statistics explained; https://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics#Acquisitions_of_citizenship:_EU_Member_States_granted_citizenship_to_almost_1_million_persons_in_2016). These new EU citizens were mainly from Africa (30% of the total number of citizenships) and Asia (21%), areas where hemoglobinopathies are highly prevalent (http://www.who.

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int/genomics/public/Maphaemoglobin.pdf). Furthermore, the above data for EU citizenships for 2016 corresponded to a 19% increase with respect to 2015. In addition, there may be an even larger and growing population of immigrants from these areas in the EU who do not have any EU citizenship and thus would not be listed above. Thus, the prevalence of SCD and sickle cell retinopathy would be expected to increase in the Western world, which in turn may have implications for health economics and for training of local ophthalmologist who may not be familiar with these conditions. For example, assuming a prevalence of up to 3% of SCD as may occur in endemic areas [1, 2] and a population of two million recent EU immigrants from such areas would mean that up to 0.03 × 2,000,000 = 60,000 individuals may be at risk of developing sickle retinopathy.

Classification of retinopathy

Organs commonly involved in SCD are the kidneys, skeleton, lungs, liver, and skin. All ocular and orbital structures can be affected by microvascular occlusions from SCD. However, the major cause of vision loss is proliferative sickle cell retinopathy (PSR) (Fig. 1). Goldberg's classification is still used to grade retinopathy severity (stages I–V) of the retinopathy [3], where stages I–II represent non-proliferative sickle retinopathy (NPSR). Similar to other retinal vascular disorders, such as retinopathy of prematurity and diabetic retinopathy, it is based on clinically significant alterations of the retinal vasculature with disease progression:

I. Peripheral arterial occlusion. This is caused by aggregation of pathological hemoglobin within erythrocytes under conditions, such as hypoxia, acidosis, and hyperosmolarity, leading to decreased deformability of erythrocytes, stagnant flow, and thrombosis.
II. Peripheral arteriovenous anastomoses (hairpin loop). This represents the initial stage of the vascular remodeling that takes place as a response to the circulatory disturbances that occur in stage I.
III. Neovascularization (sea fan). This occurs at the posterior border of non-perfusion, possibly as a result of release of angiogenic factors from the peripheral ischemic retina. A white sea fan appearance can result from auto-infarction of the neovasculature. Stage III (PSR) was subsequently subdivided, based on a prospective clinical trial of observation (35 eyes) versus retinal photocoagulation (38 eyes) [4], considering sea fan size, hemorrhage, fibrosis,

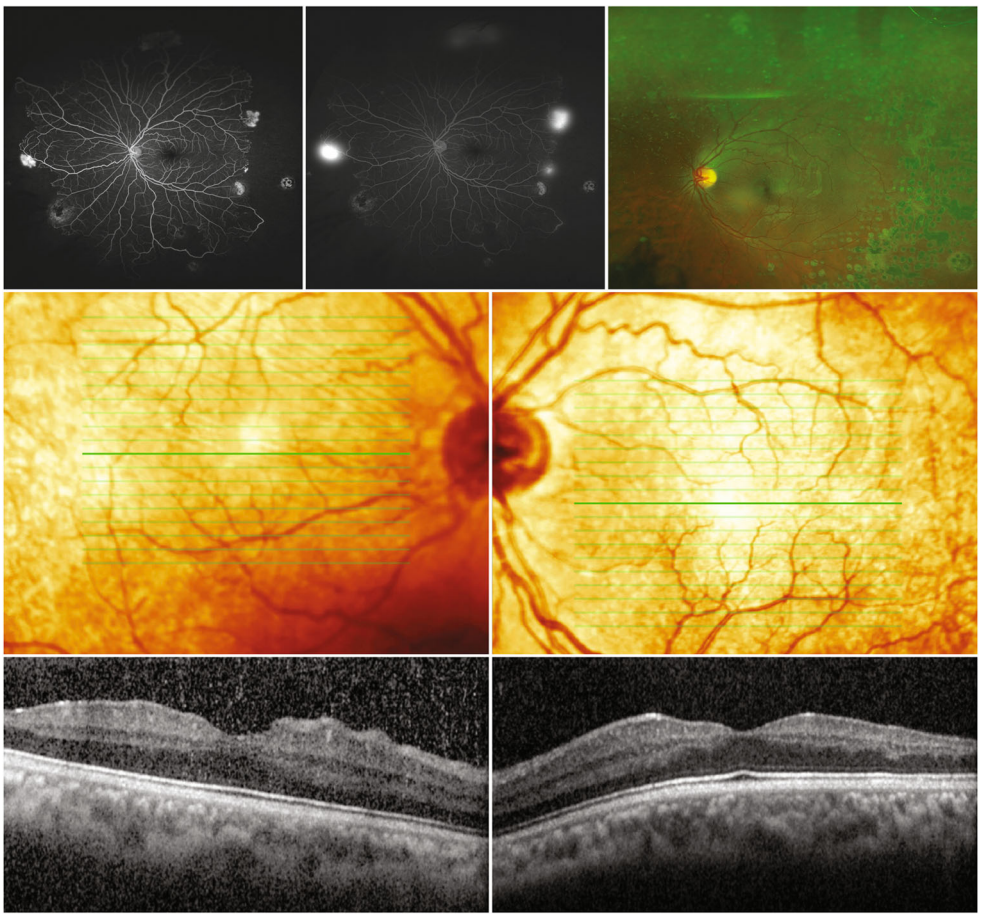

Fig. 1 Proliferative sickle retinopathy. By high-performance liquid chromatography (HPLC), isoelectric focusing, and citrate agar electrophoresis at pH 6.2, two abnormal hemoglobins are detectable, indicating heterozygosity for HbS and HbC. Upper panel, from left to right: early and late frame wide-field fluorescein angiography and wide-field pseudocolor imaging show peripheral non-perfusion and neovascularization and lasered retina with regressed neovascularization. Middle and lower panel: optical coherence tomography shows bilateral temporal macular thinning compatible with previous bilateral acute middle maculopathy

and visibility of vessels into grade A: flat sea fan with leakage < 1 disc area; grade B: elevated sea fan with hemorrhage; grade C: elevated sea fan with partial fibrosis; grade D: complete sea fan fibrosis without well demarcated vessels; grade E: complete sea fan fibrosis with well demarcated vessels [4]. Nine complications (13%) were observed, which only occurred in untreated eyes with elevated sea fan and hemorrhage (grade B) or complete fibrosed sea fan with well-defined vessels (grade E). The clinical course did not differ between treated and untreated groups concerning flat sea fan < 1 disc area (grade A) or elevated sea fan with partial fibrosis (grade C), suggesting that patients with grade A or C new sea fan classification may be observed initially [4].

IV. Vitreous hemorrhage (VH). This is commonly a result of bleeding from the neovascularizations.

V. Tractional retinal detachment (TRD) and rhegmatogenous retinal detachment (RRD). This results from degenerative changes in the vitreous over the leaking neovascularizations, leading to membrane formation and traction.

Hemoglobin mutations and structural changes

The HbVar database (http://globin.bx.psu.edu/hbvar, access date October 1, 2017) of hemoglobin (Hb) describes over 1600 variants of hemoglobin molecules. The wild-type alleles are called HBA and HBB, which are transcribed to α-globin and β-globin, respectively. In adults, hemoglobin normally consists of two subunits of β-globin and two subunits of α-globin. Each of these protein subunits is bound to an iron-containing heme, each containing an iron molecule in its center that can bind to one oxygen molecule. A single nucleotide mutation (GAG to GTG) causes the substitution of valine for glutamic acid at the sixth position of the β-globin chain in HBB, resulting in hemoglobin S (HbS). In the homozygous condition (HbSS), this mutation causes sickle cell anemia (SCA), which was frequently lethal before the advent of modern medicine, such as transfusion medicine. In the heterozygous condition (HbAS), the mutation results in a milder sickle cell trait (SCT) phenotype. A GAG to AAG mutation causes the substitution of lysine for glutamic acid, resulting in the HbC allele. Homozygous absence or decreased synthesis of the β chain from certain mutations in HBB is referred to as β-thalassemia. When present in a compound heterozygous mode with the HbS allele, this is referred to as hemoglobin sickle-beta thalassemias (HbSthal). These are the most common genotypes that may lead to SCD. Further described HbS variants include HbSD, HbSE, and HbSO (https://ghr.nlm.nih.gov/gene/HBB#conditions, accessed on 20190220).

HbSC subjects are believed to be at higher risk of developing PSR, compared with HbSS and HbSthal patients [5–11] (Table 1). The reason for this is unknown, and assessment may be biased because of differences in mortality rates and systemic treatment, such as transfusion or hydroxycarbamide [12]. However, one possible explanation could be higher hematocrit in subjects with HbSC compared with those with HbSS, leading to a higher tendency towards stagnant blood flow and thus thrombosis formation in the retinal precapillary arterioles [13]. Fox et al. observed 35 patients (40 eyes) with HbSS and 112 patients (114 eyes) with HbSC over a mean of 4–5 years [14]. In both genotypes, progression of PSR was most frequent between ages 20 and 39 years. Comparison of hematological indices, such as fetal hemoglobin (HbF) levels, in 33 HbSC patients with progression and the 17 with regression, revealed no significant differences [14].

Non-proliferative sickle cell retinopathy (stages I–II)

NPSR is commonly observed in patients with HbSS genotype. Clinical findings include peripheral retinal vascular closure/anastomoses, salmon-patch hemorrhages, iridescent spots, and black sunbursts (where the latter two may be chronic manifestation of salmon-patch hemorrhages). Central retinal changes consist of arteriovenous tortuosity, enlargement of the foveal avascular zone (FAZ), and arterial occlusions. Collectively, these are manifestations of stage I–II sickle cell retinopathy. Bilateral macular occlusive events may present with binasal field defects [15]. Electrophysiology indicates a selective early involvement of the inner retina in HbSS patients, which may be compatible with vascular occlusions in the superficial and deep capillary plexi in the inner retina [16].

Proliferative sickle cell retinopathy (stages III–V)

PSR is more frequently manifested in patients with HbSC than in other genotypes, and some degree of visual loss occurs in 5–20% of PSR eyes [11, 17, 18] (Table 1). PSR is associated with thinning of temporal macular retinal layers caused by acute paracentral middle maculopathy, which results from occlusions of the superficial and deep capillary plexi [19, 20]. Peripheral retinal vascular occlusions cause tissue ischemia and release of angiogenic mediators that promote retinal neovascularization. The hallmark in PSR patients is the sea fan configuration that occurs when the neovascularization grows anteriorly from the vascularized to avascular retina (Fig. 1). These structures have a high propensity to regress (20–60%) by autoinfarction [11, 16]. However, they may also lead to VH or TRD.

Table 1 Genotype and prevalence of proliferative sickle cell retinopathy (PSR)

	Name	Genetics	Systemic manifestations	PSR prevalence (Fekrat and Goldberg [7])	PSR prevalence (Dembélé et al. [8])	PSR prevalence (Bonanomi et al. [9])	PSR prevalence (Leveziel et al. [10])	PSR prevalence (Downes et al. [11])
HbSS	Sickle cell anemia	Sickle cell homozygote	Most severe systemically	3%	5.2%	14.64%	18.1%	14%
HbSC	Sickle cell "C" trait	Sickle cell heterozygote, with another abnormal HbC allele	Mild systemically	33%	12.4%	54.54%	54.6%	43%
HbSThal	β-Thalassaemia anemia	Sickle cell heterozygote, with another β-thalassaemia allele	Severe form systemically (β^0)	14%	9.4% ($S\beta^0$ thalassemia) 9.3% ($S\beta^+$-thalassemia)	–	–	–
			Milder form systemically (β^+)					
HbSD, HbSE, HbSO		Sickle cell heterozygote, with another abnormal Hb allele	Varies systemically	–	–	–	–	–
HbAS	Sickle cell trait	Sickle cell heterozygote, with 1 normal Hb allele	Mild systemically	–	–	–	–	

Orbital manifestations of SCD

Children with SCD may develop uni- or bilateral infarctions of the orbital bones, mainly affecting the great wing of sphenoid, with pain, headache, fever, visual acuity changes, periorbital edema, proptosis, and limited extraocular motility [21]. Bone and/or bone marrow infarction results in sterile inflammation and sub-periosteal hematoma. Exudative retinal detachment can be present in SCD-induced orbital bone infarction as a result of orbito-ocular inflammation. There may be optic nerve compression [22]. The differential diagnosis includes periorbital or orbital cellulitis, orbital abscess, or allergic reaction. Orbital wall infarction is diagnosed by computerized tomography or magnetic resonance imaging [23]. Doppler velocimetry can demonstrate elevated arterial vascular resistance in the orbit [24]. Treatment includes intravenous hydration, pain control, steroids, or even surgery when orbital compartment syndrome is present [23]. However, clinically relevant orbital manifestations of SCD are considered to be rare. On the other hand, these may be underdiagnosed considering the ischemic nature with a tendency of spontaneous improvement.

Glaucoma

Hyphaema, ghost cells from VH, or neovascularization of the angle may result in secondary glaucoma. Sickle cells may give rise to a more intense elevation of the intraocular pressure (IOP) than non-sickle cells because of reduced deformability during the passage through the trabecular meshwork, and glaucoma secondary to hyphaema may be more refractory to medical treatment [25]. The threshold for IOP lowering treatment (medical as well as surgical if needed) is low as the optic disc and the central retinal artery are thought to have a higher susceptibility to damage, due to impaired microcirculation. Oral carbonic anhydrase inhibitors, especially acetazolamide, should not be used regularly, because these may cause dehydration and acidosis, leading to increased sickling of erythrocytes [13].

Genetic and systemic risk factors of sickle cell retinopathy and proliferative sickle cell retinopathy

Malaria is or was highly prevalent in areas where SCD is common, and it is believed that heterozygosity for the sickle cell allele may confer malarial resistance and hence, a selective advantage [26]. As for other recessive disorders, consanguineous marriage increases the risk of SCD in endemic areas.

Despite the less serious systemic consequences of HbSC subjects, they are believed to be at higher risk of developing

PSR, compared with HbSS and HbSthal patients [5, 6]. The reason for this is unknown, and assessment may be biased because of differences in systemic treatment, such as transfusion or hydroxycarbamide or different mortality rates [12]. One possible explanation could be higher hematocrit in subjects with HbSC compared with those with HbSS, leading to a higher tendency towards stagnant blood flow and thus thrombosis formation in the retinal precapillary arterioles [13]. On the other hand, there seems to be no link between rheological factors (plasma and serum viscosity, whole blood viscosity, and erythrocyte filterability) and the development of PSR [14, 27, 28].

With increasing prevalence of type 2 diabetes mellitus (DM) worldwide, a large cohort of people may have concurrent DM and SCT, considering that the prevalence of SCT may approach 20% in endemic areas [1]. It would be reasonable to hypothesize that coexisting SCT and DM may increase the risk of microvascular complications. However, Al Harbi et al. conducted a retrospective analysis of the rate of PDR and/or diabetic macular edema in 100 patients with SCT and DM and an equal number of age-matched controls with DM but no SCT [29]. The rate of PDR and/or diabetic macular edema was significantly higher in the controls (95%) than in patients with SCT (58%, $p < 0.001$) [29]. Thus, the proangiogenic molecules that play a role in disease progression may differ between SCD and DM. On the other hand, TRD was more frequent in patients with SCT than in controls (26% vs 11%, $p = 0.006$) [29]. One possibility is that temporal macular ischemia, similar to that seen after acute middle maculopathy in PSR, may contribute to the formation of TRD in patients with SCT and DM.

Age is considered as one of the risk factors of progression to PSR, and the risk of PSR below 10 years of age is very rare. Talbot et al. conducted serial examinations in 389 children aged 5–13 years with SCD. Peripheral retinal vessel closure was present in approximately 50% of children with SS and SC genotypes at age 6 years and increased to affect 90% of children by age 12 years. Proliferative retinopathy occurred only once in an 8-year-old boy with SC disease, despite 592 patient years of observation [30]. A retrospective analysis of 258 children with SCD identified 54 children with Sickle cell retinopathy [31]. Pain crisis, male gender, and splenic sequestration were clinical risk factors that were associated with sickle cell retinopathy in these pediatric patients [31]. Of the 54 children with sickle retinopathy, 11 (4.3%) had PSR, with a mean age at diagnosis of 12.7 years (range 10–17 years).

PSR was associated with older age (> 35 years) in a London cohort of 189 patients with SCD [32]. Visual impairment was related to the presence of PSR; however, it was not related to Hb genotype [32]. The association between age and progression towards PSR was further corroborated in a recent retrospective study of 296 patients with SCD, where male gender and older age were associated with PSR [33].

Sickle cell retinopathy has phenotypic variability even among individuals with the same genotype. A cross-sectional study in a Brazilian SCA cohort showed that IL-6-597G>A is associated with a higher likelihood of retinopathy [34]. A Greek study determined that the endothelial nitric oxide (NO) synthase T786C polymorphism was more common in HbSS and HbSβ0 patients with retinopathy in comparison with the G894T polymorphism [35]. Environmental factors may confound these studies. For example, Mehta et al. described a patient with SCT who developed PSR after mild ocular blunt trauma [36]. The reported prevalence of PSR in various genotypes is summarized in Table 1.

Diagnosis

Cation-exchange high-performance liquid chromatography (HPLC), in conjunction with electrophoresis, is the main diagnostic method [37].

Molecular genetic diagnosis has been described for prenatal and neonatal screening [38, 39].

Diagnosis of retinopathy is based on typical clinical findings in the presence of a history of SCD or positive laboratory findings as described above.

Differential diagnoses

A wide spectrum of diseases that result in either macular ischemia, or peripheral retinal neovascularization, should be considered in the differential diagnosis [40–45] (Table 2). On the other hand, sickle retinopathy should be considered as a differential diagnosis in retinal vascular disease. A prior history of SCD helps rule out many other conditions, although it is possible for some other conditions to occur simultaneously with NPSR/PSR.

Advances in sickle cell retinopathy ocular biology

Identifying molecules associated with PSR development may help in their use as therapeutic targets. Angiopoietin-like 4 (ANGPTL4) has been detected in neovascular tissue and in the ischemic inner retina in PSR, but not in control eyes. Its presence has been well documented in other vasoproliferative ocular condition like diabetes retinopathy, retinal vein occlusion, and age-related macular degeneration, and only recently, it was established in PSR [46]. Elevated expression of ANGPTL4 has also been observed in the aqueous and vitreous of PSR patients compared with controls [46], suggesting that it may contribute to PSR development (Fig. 2). Knowledge regarding the origin and retinal distribution of

Table 2 Differential diagnosis of sickle cell retinopathy

Differential diagnoses	
Macular ischemia/infarction	Diabetic retinopathy
	Retinal vascular occlusion, e.g., posterior ciliary artery thrombosis
	Retinal embolization, e.g., talc retinopathy, internal carotid artery embolism
	Infectious retinopathy, e.g., toxoplasmosis, dengue (Yip et al. [40]).
Ischemic vascular disease	Proliferative diabetic retinopathy
	Central/branch retinal vein occlusion
	Ocular ischemic syndrome
	Radiation retinopathy
	Retinopathy of prematurity
	Familial exudative vitreoretinopathy
	Eales' disease
	Blood dyscrasias, e.g., chronic myeloid leukemia, deficiency of protein C, or protein S
Ischemic inflammatory disease	Sarcoidosis
	Retinal vasculitis
	Intermediate uveitis
	Acute retinal necrosis
Miscellaneous	Incontinentia pigmenti. Vascular occlusive phenomena of small vessels causing avascular peripheral retina and peripheral neovascularization.
	Autosomal dominant vitreoretinochoroidopathy. Associated vascular abnormalities, e.g., microaneurysms, vascular leakage, arteriolar attenuation, venous beading, venous sheathing, venous occlusion, focal venous staining, and retinal neovascularisation
	Chronic rhegmatogenous retinal detachment with macrocyst formation, peripheral capillary non-perfusion, telangiectasias, and retinal neovascularization. Neovascularization posterior to the retinal holes (Bonnet [41]), which could have a seafan configuration (Georgalas et al. [42]).
	Non-rhegmatogenous retinal detachment with secondary neovascularization, e.g., Coats disease, peripheral retinoschisis (Pearson and Jagger [43]).
	Scleral buckle. A tight encirclage may impair the long posterior ciliary arteries and choroidal venous drainage (Duguid et al. [44]).
	Retinitis pigmentosa (Kadayifcilar et al. [45]).

proangiogenic factors may be relevant for proper targeting and delivery of retinal laser treatment. Pigment epithelium derived factor (PEDF) was elevated in HbSC patients with PSR [47]. Increased ICAM-1, VCAM-1, and P-selectin immunoreactivities have also been observed in PSR subjects [48].

Subclinical retinopathy and recent imaging modalities

Ultra-wide-field fluorescein angiography (UWFA) visualizes vascular abnormalities in the far periphery of the retina, typical of sickle cell retinopathy. Pahl et al. conducted a cross-sectional study in pediatric patients (age 10–19 years old) with SCD, demonstrating that all 24 eyes examined by UWFA had sickle cell retinopathy, even if this had not been detected on biomicroscopy. Findings included peripheral arterial occlusion in four of the 24 eyes and peripheral arteriovenous anastomoses in the remaining 20 eyes [49].

In PSR, UWFA may prove to be useful in guiding laser treatment to ischemic areas. Furthermore, by enabling the calculation of an ischemic index based on imaging of the whole retina, a quantitative approach may become possible in the future management of sickle retinopathy [50, 51].

Spectral-domain optical coherence tomography and optical coherence tomography angiography (SD-OCT and OCT-A) identified abnormal macular thinning and flow voids in the superficial and deep retinal capillary plexus in 20% of eyes that had been unobserved by biomicroscopy. These findings suggest that pediatric sickle retinopathy may be more prevalent than previously suspected [49, 52]. Temporal macular thinning caused by paracentral acute middle maculopathy may be the result of occlusions at the level of the deep retinal capillary plexus (Fig. 1) [53–55]. These lesions are not detected by fluorescein angiography. Sickle cell patients with focal

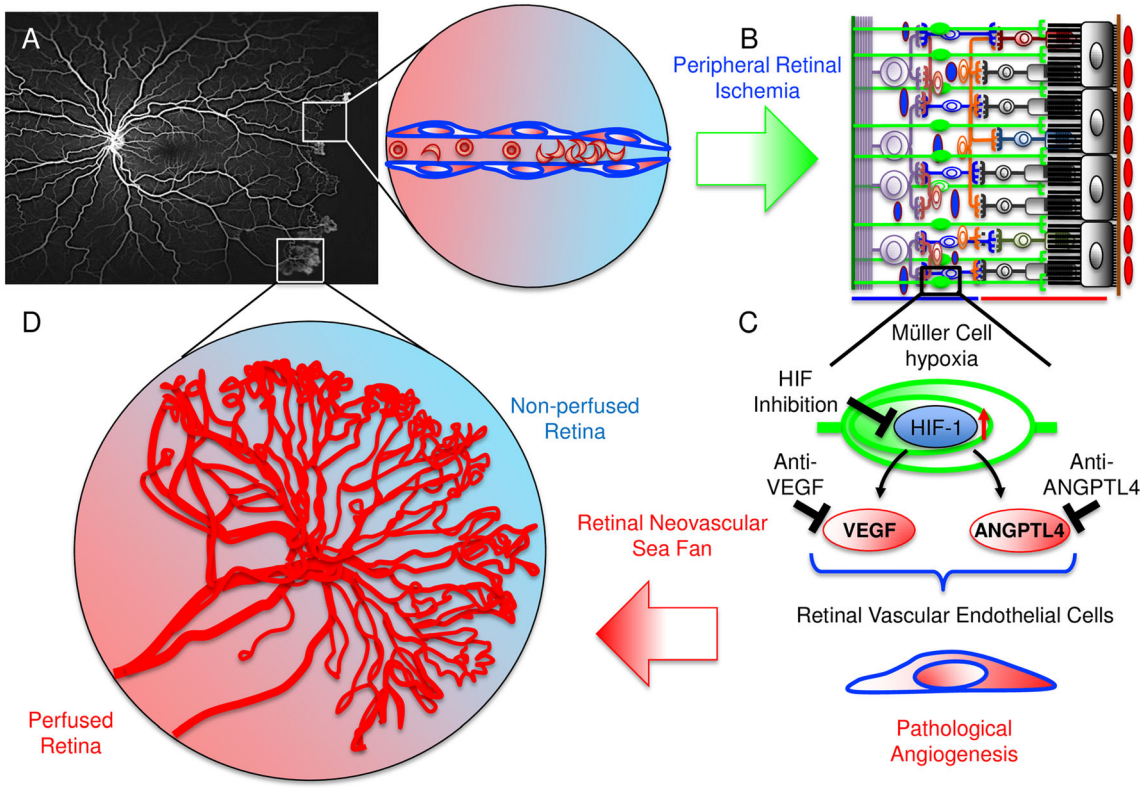

Fig. 2 Figure reprinted from Jee et al. PLoS One 2017 (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0183320#pone-0183320-g005) courtesy of Dr. Akrit Sodhi, Wilmer Eye Institute [46]. Schematic illustration depicting the progression from peripheral non-perfusion to the development of neovascular sea fans in proliferative sickle retinopathy

macular thinning identifiable on SD-OCT have significantly decreased retinal function on microperimetry compared with subjects without focal thinning or controls [56]. Such maculopathy may be a marker of PSR and potentially of the severity of SCD.

The development and use of SD-OCT and OCT-A suggest that significant macular vascular changes occur early in the natural history—even in asymptomatic patients. Identification of subclinical retinopathy will help identify those patients who need to be screened.

Thus, further prospective study is warranted, using wide-field imaging, SD-OCT, and OCT-A to determine prognostic markers in sickle retinopathy and optimal laser delivery for PSR.

Prophylactic therapy

Similar to diabetic retinopathy, systemic management has a significant impact on retinopathy development and progression. HbF usually disappears from the blood of infants after about 6 months; however, it is found in certain conditions, such as myeliod leukemia and sickle cell crisis. Hydroxycarbamide promotes the production of HbF, which does not polymerize and deform red blood cells like the mutated HbS and thus has a favorable effect in children in preventing retinopathy [57]. In sickle cell hemoglobin therapy, the goal is to dilute the HbS containing erythrocytes to ensure better tissue oxygenation and thus prevent vascular occlusion. Children with a HbF < 15% had 7.1-fold higher odds of developing retinopathy, and those with retinopathy had lower HbF levels compared with children without retinopathy. Likewise, reducing HbSS concentration by exchange transfusion has also been reported to be successful [58, 59]. Thus, the presence and type of systemic treatment, such as hydroxycarbamide, may need to be taken into account when studying the retinal response to local treatment such as laser. On the other hand, Fox et al. compared hematological indices, such as fetal hemoglobin (HbF) levels, in 33 HbSC patients with progression to PSR and the 17 with regression of PSR and found no significant differences [14]. This implies that the biological mechanism that results in progression towards PSR may be other than just vascular occlusion and ischemia and may in addition require the activation of specific proangiogenic molecules.

Hyperbaric oxygen therapy (HBO) may reverse the pathology and has been described to improve the visual acuity in a patient with central retinal artery occlusion associated with SCD [60]. HBO therapy increases arterial pO2, thereby potentially reversing erythrocyte sickling in the retinal and optic nerve microcirculation. However, a simultaneous exchange

transfusion was administered, which may on its own have had beneficial effects on the retinopathy through reduction of sickling, thereby confounding a potential effect of the HBO [60]. HBO administration has also been administered during scleral buckling surgery for RRD associated with SCD, with reportedly favorable outcome [61]. However to date, there have been no prospective controlled studies using HBO in the management of complications associated with sickle cell retinopathy [60, 61]. A potential cure the hematological disease as such, for example through gene therapy or stem cell transplantation, would prevent retinopathy and could therefore be considered as primary prevention or prophylaxis. Retinal laser therapy or intravitreal anti-angiogenic therapy may be seen as secondary prevention, for example to prevent VH in the presence of PSR.

Screening

It was suggested that serial examinations may be done biannually for eyes with normal findings [62]. The development of PSR is believed to be highly unlikely before age 10 years [31]. For example, Rosenberg & Hutcheson screened 258 pediatric patients with SCD with dilated fundus examination [31]. Of these, 54 (20.9%) had retinopathy, and 11 (4.3%) had PSR. The average age of patients with any retinopathy was 13.0 years (range, 6–18 years). Patients with PSR were slightly older (mean, 14.18 years; range, 11–17 years) than those with NPSR (mean, 12.72 years; range, 6–18 years), but the difference was not statistically significant [31]. Thus, a consensus report (Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014: Guide to Recommendations, available on https://www.nhlbi.nih.gov/sites/default/files/media/docs/Evd-Bsd_SickleCellDis_Rep2014.pdf accessed on 20190218) 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. The aim of retinopathy screening is to detect PSR and consider treatment for example photocoagulation before complications, such as VH or TRD or retinal vascular occlusions with visual loss occur. In terms of diagnostic screening, DNA screening in newborns at risk, for example with a positive family history of SCD, has been suggested [38, 39].

Treatment

Anemia that may be associated with hemoglobin disorders may require blood transfusions. If so, patients may need therapy with iron chelating agents, to reduce toxicity to multiple organs from iron overload. However, iron chelating therapy may result in maculopathy as a side effect of the medication, possibly related to chelation of other essential trace substances, such as copper and zinc leading to intracellular deficiency of these substances in the retinal pigment epithelium (Fig. 3). However, there may be a direct toxic effect to the RPE from the medication (Fig. 3) [63].

Laser photocoagulation

Due to the risk of vitreous hemorrhage and retinal detachment, scatter photocoagulation may be considered in order to prevent visual loss and VH if the sea fans do not autoinfarct (Fig. 1). This is based on two clinical trials [64, 65] that were subsequently analyzed in a Cochrane review comprising a total of 341 eyes [66]. The review corroborated that laser treatment may prevent the occurrence of VH, with the protective effect being greater with feeder vessel laser treatment compared with scatter photocoagulation [66]. However, the feeder vessel technique of laser treatment is considered as being potential harmful, sometimes leading to vitreous hemorrhage and retinal breaks and has been abandoned [66]. Moreover, the Cochrane review was based on two studies [64, 65] performed in the early 1980s and 1990s, thus the results may not apply considering recent development of laser technology [66]. Furthermore, none of the studies used circumferential scatter laser—only limited laser techniques, such as sectorial scatter and feeder vessel photocoagulation. There was no significant difference regarding regression of PSR or rate of development of new PSR, which was the primary outcome, between the treatment and control groups, over a mean follow up duration of 47 and 42 months, respectively [66]. The reason why there was no clear benefit of laser compared with observation in PSR may thus have been related to a lack of consensus regarding how to apply the laser treatment. Recently, the study of autopsy eyes with SCD suggested that hypoxia-inducible factor 1 (HIF-1α) and vascular endothelial growth factor (VEGF) are being produced not only in the endothelial cells lining the neovascularizations and in the inner retina of the peripheral non-perfused retina distantly from the neovascularizations but also to some extent in a 2-mm wide transitional zone posterior to the non-perfused periphery [67]. This may support broad application of peripheral laser, such as circumferential scatter covering the entire area from the Ora Serrata anteriorly up to 1–2 mm posteriorly to the neovascularization for the treatment of PSR [67]. Recent development in wide-field imaging enables targeted laser to ischemic retina, which may be beneficial. However, this has not been examined to date in any prospective trial.

Intravitreal injection of anti-vascular endothelial growth factors

Current evidence is based on the use of bevacizumab with one exception describing the use of ranibizumab [68]. Similarly to proliferative diabetic retinopathy, intravitreal

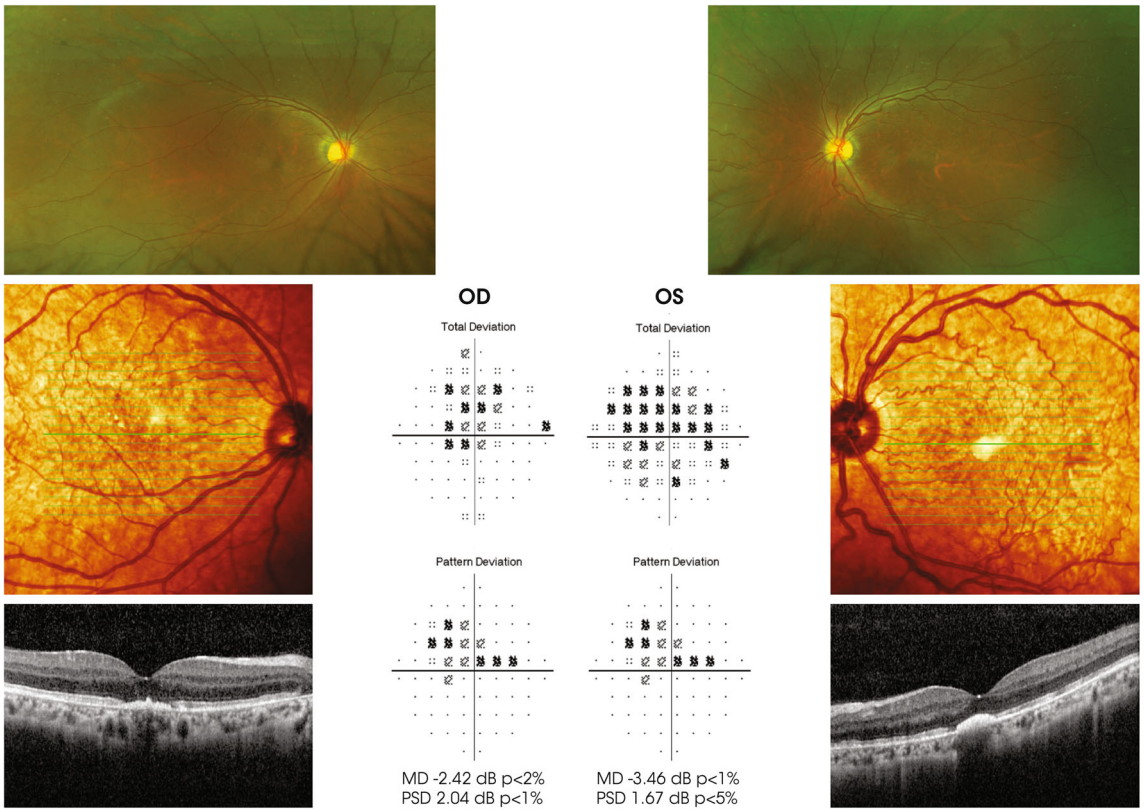

Fig. 3 A patient with known beta-thalassemia that had received blood transfusions for anemia and iron chelating medication for many years (Desferioxamin and Desferal). Vision was reduced. However, there was no nyctalopia or photophobia. Upper panel: Color fundus images show subtle pigment alterations in the maculas. Lower panel, left and right: Optical coherence tomography shows bilateral irregularities and accumulation of material at the level of the retinal pigment epithelium-outer retina complex in the macula. Center: visual field defects are demonstrated

administration of bevacizumab therapy may lead to regression of neovascularization. Intravitreal bevacizumab can be used as a pre-surgical adjunctive agent to decrease the risk of intraoperative bleeding and facilitate dissection of sea fan neovascular structures [69–71]. Although preoperative bevacizumab may be efficient, secondary hyphaema, a few days post-injection, is a possible complication [72]. Cai et al. recently described five eyes of five patients with PSR that were managed with intravitreal bevacizumab therapy over a 13-year period [73]. Four patients had HbSC disease and one had HbSthal disease. Four of the patients were treated for recurrent vitreous hemorrhage, and one was treated for new peripheral sea fan neovascularization. The vitreous hemorrhage cleared starting from 2 weeks after the treatment, and all patients showed a partial regression of the neovascularizations. Two of the patients had documented recurrent vitreous hemorrhage during the period of follow-up after an initial injection [73]. Clinical trials directly comparing the effect of intravitreal injections of antiangiogenic agents with scatter laser photocoagulation PSR are warranted.

Vitrectomy

Indications for pars plana vitrectomy (PPV) in PSR are visually significant non-clearing vitreous hemorrhage, bilateral vitreous hemorrhage, vitreous hemorrhage in a monocular patient, or a retinal detachment (Supplemental Fig. 1 and Video 1) [74]. Scleral buckle surgery (SBS) is known to reduce retinal blood flow and alter perfusion of anterior structures, e.g., anterior choroid, ciliary body, and ciliary processes [75]. It has also been implicated in anterior segment ischemia. Therefore, a scleral buckle should not be encircled overly tight in PSR, where there is a compromised perfusion to start with, due to the ischemic nature of the disease.

A retrospective, interventional case series of PSR patients managed with PPV over a 12-year period exhibited success in improving vision postoperatively in patients with vitreous hemorrhage or epiretinal membranes [74]. Nevertheless, there was reduced success in patients with recurrent TRD or RRD. The rate of surgical complications in patients with PSR was as high as 50% for traction/RRD [74]. Four of the eight patients developed recurrent detachments and required a second operation. All retinas were attached at last follow-up, and visual

acuity was 20/400 or better in all eyes. No cases of anterior segment ischemia were encountered [74].

Segmentation techniques were recommended over delamination techniques for dissection of peripheral neovascular fibrovascular tissue and epiretinal membranes in PSR [64, 76]. This was because these structures were strongly adherent, and removing them using delamination could risk iatrogenic tears. However with recent improvement of instrumentation and intraoperative OCT, delamination may be feasible (Supplemental Fig. 1 and Video 1).

General anesthesia (GA) would be ideal due to its provided optimal intraoperative pain control; however, this may risk intraoperative systemic sickle cell crisis. A hematological consultation should be obtained before surgery, and patients should be well hydrated and oxygenated in the perioperative period [13]. In cases where GA is contraindicated, sub-Tenon block is preferable to retrobulbar block in SCD patients as such patients have a theoretical risk of orbital compartment syndrome from orbital sickling events [77]. It is essential to minimize prolonged periods of significant rise in IOP during the surgery because of the risk of arterial occlusion.

Hematopoietic stem cell transplantation has the potential to cure SCD as such, including preventing any retinopathy; however, such treatment may be associated with complications including infertility and debilitating graft-versus-host disease and a mortality rate of 5–10% in the short term [78, 79]. Gene therapy for hemoglobinopathies has been described in single cases using transplantation of autologous hematopoietic stem cells genetically modified with a lentiviral vector expressing a globin gene under the control of globin transcriptional regulatory elements [80]; however, an altered bone marrow microenvironment that reduces the efficiency of stem cell harvesting as well as engraftment still limits its general application.

Conclusion and further directions

Recent advances in ocular imaging, such as SD-OCT and OCT-A, have revealed the microstructural features of sickle cell retinopathy, enabling improved diagnostic precision and earlier diagnosis. Maculopathy with inner retinal thinning may be a marker of PSR. The vascular growth factor ANGPTL-4 has been identified as a possible mediator of the progression from NPSR to PSR. Retinal laser therapy for the latter is often administered in order to prevent complications of PSR, such as VH; however, the evidence in favor of laser is not very strong. A more extensive circumferential laser targeting the entire peripheral ischemic retina may be useful; however, such an approach has not been studied in any randomized trials to date. Targeted laser to ischemic retina is possible with the recent development of wide-field imaging. New development of microsurgical vitreoretinal equipment with exact control of intraoperative IOP, including valved trocar vitrectomy systems, may be of benefit in improving the outcomes of surgery for complications associated with PSR. Inhibition of HIF-1α or both VEGF and ANGPTL-4 could be an effective approach for the treatment of PSR. Stem cell transplantation and gene therapy are potentially curative treatments under development that may prevent any retinopathy from developing. Whether these advances may lead to improved management and outcomes of treatment of sickle retinopathy remains unanswered, and further study is needed.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the study was conducted.

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