Review Article

Capsula Eburnea
a multidisciplinary biomedical journal for young doctors

SICKLE CELL RETINOPATHY

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Abstract
Occlusion of small blood vessels in the eye, retinal neovascularization and its consequences occur in high frequency in patients with sickle cell disease. Neovascular sea fans arise at the interface of perfused and nonperfused portions of the retina. Although some lesions undergo spontaneous autoinfarction, most show progressive growth, resulting in vitreous hemorrhage and retinal detachment. The emergence of neovascolarization is stimulated by the production of vascular growth factors and immunoreactivity for these factors is greater within neovascularization than in adjacent retina and in non perfused peripheral retina. All these lesions can be observed directly with an ophthalmoscope and indirectly with fluorescein angiography. The differential diagnosis of the neovascularization with other ischemic and inflammatory diseases is necessary. The usual goal of management is the early treatment of stage III lesions with laser photocoagulation and cryotherapy; pars plana vitrectomy or scleral buckling are avoided unless it is absolutely necessary.

Keywords: Hemoglobinopathies, Retina, Ischemia, Red Blood Cells

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Received: January 31th, 2010
Revised: February 12th, 2010
Accepted: February 15th, 2010

Language of the Article: English.

No conflicts of interest were declared.

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ISSN: 1970-5492

DOI: 10.3269/1970-5492.2010.5.4

Introduction

Sickle cell disease is a haemolytic disorder caused by the synthesis of abnormal haemoglobin molecules that leads to irregular crescent-like or sickle shape of the red blood cells. This abnormality leads to blood flow disturbances, chronic haemolytic anaemia and other systemic complications. The disorder is an autosomal recessive one and the red blood cells acquire the sickle shape due to decrease oxygen concentration or other physiological stress.
The condition is caused by the erythrocytes assuming abnormal shapes due to the production of an abnormal haemoglobin molecule, which then polymerises under acidic or hypoxic conditions (1). The haemoglobin molecule, HbC (2), is the product of a single point mutation in the haemoglobin molecule HbA. In the normal adult, HbA contains 2 alpha chains and 2 beta chains; however, the mutation causes amino acid to substitute the glutamic acid for valine at the sixth sequential position of the beta haemoglobin subunit (3).
The presence of the sickle-shaped cell results in vaso-occlusion in the body's entire organ system. There are four variants of the condition. The first, a homozygote condition which affects approximately 0.4% of the black population, is sickle cell anaemia (HbSS) results when a subject inherits the Haemoglobin-S gene from both parents. Inheriting one Haemoglobin-S and one Haemoglobin-C gene will result in HbSC disease (4); inheriting one sickle gene and one normal results in HbAS, the sickle cell

condition which affects 8-10% of the black population; and inheriting a sickle cell gene and a beta-thalassemia gene causes Sickle cell-thalassemia (5).
In HbSC disease and HbSbeta-thalassemias, the sickle cell trait may be manifested into something like sickle-cell disease under conditions of stroke, hypertension, hypercholesterolemia or trauma (6). The ocular effects of the disease itself- initially microvascular occlusion, leading to retinal hypoxia, ischemia, infarction, neovascularization and fibrovascularization- are attributed to the sickling of red blood cells within small vessels (7).

Clinical features
The subject, in whom symptoms are not necessarily manifested at an early stage, risks permanent visual damage due to vaso-occlusion, which can affect all the vascular beds in the eye including the conjunctiva, anterior segment, retina and choroid. The disease can however be detected by examining the eye carefully. Vasoproliferative changes can reveal sickle haemoglobinopathies and have been recorded to include altered conjunctival vasculature, hyphema, retinal "salmon patch" hemorrhages, retinal "iridescent spots," retinal "black sunbursts" and various abnormalities of the retinal vasculature, macula, choroid, and optic disk. In fact, isolated dark red curved or corkscrew vascular fragments, under close examination will also be seen endothelial proliferation and aggregation of red blood cells in distal portions of capillaries and dilatation and thinning of the proximal segments of the vessels, will be observed in the inferior bulbar conjunctiva (8). The conjunctival alterations in HbSS patients will be more prominent than in HbSC patients and AS patients, affected by the sickle cell trait, the latter of which very rarely show any conjunctival change (9). A further condition known as hyphema may occur during trauma or surgery, if blood occurs in the anterior chamber of the eye, where normally one would find aqueous humour. The metabolizing erythrocytes and leukocytes use oxygen and liberate CO2 and lactic acid, causing hypoxia, hypercarbia, and acidosis. This leads to the sickling of erythrocyte cells in the anterior chamber, meaning that they cannot pass through Schlemm's canal, and so aqueous humor cannot escape they eye. The pressure in the eye therefore increases and thus the pressure of vascular perfusion is reduced. A slight reduction in the perfusion pressure can cause severe risk of occlusion in the artery (10). The salmon patch hemorrhage originally red in color, which is found in the superficial retina within the mid-peripheral retina, is the result of the bursting of vascular walls which are already weakened by ischemia and occlusion (11). If resorption of the hemorrhage occurs, the retina may appear undamaged, although normally there will be a small indentation visible, the result of the thinning of the inner retina. Under ophthalmoscopy, in this indentation are visible small yellowish spots, observed in observed in 33% of HbSC patients, 18% of HbSThal patients, and 13% of HbSS patients (12). The black sunburst lesion (13), which affects 41% of HbSC patients (12), 35% of HbSS patients and 20% of HbSThal patients, is a black patch 0.5 to 2mm in diameter, is the result of the hyperplasic retinal pigment epithelium migrating within the retina. It is accompanied by iron deposits, hemosiderin-laden macrophages, and pigment deposition.
There is generally no visual symptom of the posterior pole, even if it is affected by increased tortuosity (13). This condition rarely occurs in HbAS and HbSThal patients, but it may affect up to 47% of HbSS patients and 32% of HbSC patients. Repeated occlusion in the peripheral retina may result in the recession of the most vascular arcades, causing a ischemic peripheral retina (14).
The macular depression, sometimes accompanied by a reduction of visual acuity, is the thinning of the inner retina (15). Within the macula, visual irregularities may also occur- microaneurysmal dots, dilated precapillary arterioles and capillary segments, nerve fiber layer infarcts, and hairpin-shaped venous loops with adjacent capillary dropout. One or all of these symptoms is found in 32% of HbSS patients, 36% of HbSC patients and 20% of HbSThal patients.
Occlusion in the posterior ciliary arterial circulation also causes choroidal occlusion, the effects of which include impacted erythrocytes, increased fibrin, and platelet-fibrin thrombi (16,17); additionally angioid streaks may form, orange-red or brown streaks that emanate radially in the fundus from the optic nerve and probably result

from calcification and brittleness of Bruch's membrane. Causing a far lower risk to the vision, vascular changes at the optic disk, consisting of dark, dilated capillary vessels that can be observed with fluorescein angiography, can result in the vessels opening and closing intermittently (18). Proliferative sickle retinopathyn is initialized by peripheral retinal arteriolar occlusion, which occurs in the vicinity of Y -shaped bifurcations and produces localized ischemia (19). Vascular growth factors are therefore stimulated and sea-fans, neovascular fronds, appear. These are liable to vitreous hemorrhages, which results in the formation of tractional vitreous membrane and the detachment of the retina (14).
The most widely-recognized classification scheme is that of Goldberg and his colleagues, who detail in a five step plan the stages of proliferative sickle retinopathy:
- Stage I: peripheral arteriolar occlusion;
- Stage II: artero-venous anastomoses occurs at the border between the vascularized and the ischemic peripheral retina. The anastomoses indicate the enlargement of pre-existing vessels with intact blood-retinal barrier properties rather than true neovascularization (20);
- Stage III: neovascularization accumulate towards the ischemic pre-equatorial retina (14). They are mostly found in the superotemporal quadrant, then in the inferotemporal, superonasal and inferonasal quadrants respectively. They are characterized by multiple feeding arterioles and draining venules and probably origin from break through the internal limiting membrane of retina, due to multiple buds of angiogenesis (21). They may be accompanied by lumens ensheathed with pericytes, autoinfarcted segments and actively growing blood vessels. Intravenous fluorescein angiography or angioscopy during standard ophthalmoscopy can reveal the loss of the blood-retinal barrier, indicated by the presence of leaked intravascular fluorescein dye (14);
- Stage IV: mostly in HbSC patients, the sea fans migrate into the vitreous cavity, where traction may cause their vascular channels to bleed. A vitreous hemorrhage therefore occurs;
- Stage V: tractional or rhegmatogenous retinal detachment, occurring almost exclusively in HbSC patients and rarely in HbAS (22) or HbSS (23) patients, is caused by chronic vitreous hemorrhages and plasma transudation and may result in vitreous bands and condensed contactile membranes.
In some cases, probably induced by chronic hypoxia and ischemia, the sea fans may autoinfarct- sometimes only in one region of the eye, causing them to regress (11). The reasons for this are not fully understood but it is believed that their high expression of leukocyte-endothelial cell adhesion molecules and greatly increased numbers of neutrophils are factors. Neovascular lesions are therefore obliterated to reduce the risk of damage (24).

Pathogenesis
It is still not fully understood why the conditions leading to the retention of sickle erythrocytes in the tissue occurs. The study of Gerard A. Lutty has showed that in both tissues hypoxia-mediated retention of dense red cells and adherence of red cells in reticulocyte-rich fractions occurs after cytokine stimulation (25). Cytokines like TNF-α and IL-1α up-regulate leukocyte adhesion molecule expression by vascular endothelial cells (26,27), as VCAM-1. The interaction between VCAM-1 and VLA-4, an integrin expressed by reticulocytes, leads to the adherence of dense cells and reticulocytes to both macrovascular and retina microvascular endothelial cells in sickle cell patients, because they have elevated levels of TNF-α IL-1α (28-31). Their study demonstrate that VLA-4 antagonists can prevent sickle cell retention in choroid due to the increase of cytokine levels and that the retention process is dependent on expression of VLA-4 by some sickle red cells (31,32) and on the interaction VLA-4/ VCAM-1 (33). The study concluded that the choroidal retention of sickle cells is caused by the same mechanism by which sickle cells are retained in the retina: the retention increases after a few minutes exposure to decreased arterial pO2 (34), inducing a mechanical obstruction due to non deformability of these cells. Then, when the retinal vasculature is stimulated by TNF -α, VLA-4 positive red cells adheres to endothelium. If the VLA-4 positive red cells then adhere to activated endothelium, the irreversible sickle cell may be trapped, leading to hypoxia and the increase of the

dense red cells retained in these vascular segments.
During the study, it was found that the sickle cells was greater in choriocapilleries than in the retina This might be a factor for high levels of angioid streaks and choroideal neovascularizations in the patients. The angioid streaks are probably the result of rupturing in the thickened and brittle Bruch's membrane, which leads to fibrovascular invasion and RPE detachment (35-38).
A further study by Jingtai Cao and colleagues revealed that angiogenic factors, that stimulate the origin of neovascularization, may function in an autocrine way, since their immunoreactivity was greater in the neovascularization than in adjacent retina and in non perfused peripheral retina. Furthermore, the area at the border of perfused and non perfused peripheral retina is not, as was previously thought, hypoxic, but has comparative VEGF immunoreactivity (39). Other in vitro study therefore concluded that VEGF immunoreactivity may not in fact have been produced in a paracrine manner by adjacent, hypoxic sensory retina(40).

Diagnosis
The disease may go unnoticed for many years, as symptoms do not necessarily manifest at first. Eye-examination by an ophthalmologist normally reveals the traces of the disease, and to reduce the risk, the disease should be detected in childhood with regular examination continuing throughout adulthood of the visual acuity, intraocular pressure, anterior structures and posterior and peripheral retina. In the case that a normal ocular examination is not sufficient, B-scan ultrasonography may be used, especially in the case of vitreous hemorrhages (41). Other diseases, such as ischemic retinopathies and other inflammatory diseases may accompany the original diagnosis (42). (Table 1. Differential diagnosis of the neovascularization of sickle cell retinopathy).

Treatment
The treatment varies depending on the severity of the symptoms: a small sea fan will normally just be closely monitored until a hemorrhage occurs; if hemorrhage has already occurred or the sea fans are large or the neovascular tissue has expanded rapidly, therapeutic intervention will be carried out. Stage III of Golding's treatment is attempted before measures such as laser photocoagulation and cryotherapy, in the hope of reducing the risk of serious treatment, as pars plana vitrectomy or scleral buckling, and thus the risk of complications(43).
Direct heavy laser treatment of nutrient arterioles and subsequently draining venules in the majority of cases causes the closure of sea fans, thus reducing the possibility of vitreous hemorrhage and secondary visual loss (44). Of the two types of laser used, argon and xenon, the argon is the most popular choice because it is less likely to injure Bruch's membrane. The venule is drained after the feeder arteriole has been segmented- however, this phase of the process requires high power and has been linked to further complications such as chorioretinal neovascularization, chorio-vitreal neovascularization, and retinal detachment (45).
A further potential treatment with a low complication risk is scatter photocoagulation, which may reduce the risk of vitreous hemorrhage and secondary visual loss in patients with proliferative disease. In this process, the spots are placed one burn width apart and the retinal production of antiogenic factors, initialized by prior vaso-occlusion, is reduced (30) Chorioretinal adhesion is reduced by the laser scar, which minimizes the extent of retinal detachment. If the neovascular tissue is not regressed and there is imminent risk of developing vitreous hemorrhage, the clinician may pursue aggressive feeder vessel photocoagulation. Scatter treatment, which is low-risk, is a preferred form of precautionary treatment whenever neovascularization occurs, in all except HbSS patients over 40 years old, 86% of who tend to remain stable or demonstrate regression of neovascular tissue (46). The patient should be monitored regularly following the treatment, in order to observe the regression or progression of neovascular disease.
Transconjunctival cryotherapy is used if the retina is not visible enough for the above-mentioned processes. On average, 70% of sea fans may be treated in this way (47).Attention during the process is crucial, as retinal breaks and detachment may result if the process has to be carried out again in the same area (48).

If, after 6 months monitoring of new vitreous hemorrhages, the view is not good enough that cryotherapy or laser treatment can provide adequate treatment, vitrectomy surgery or scleral buckling surgery are implemented. The risk of complications both during and after the operation is higher, but if the patient shows early signs of retinal detachment, surgery must go ahead. In cases of rheumatogenous detachments, scleral buckling must be implemented, whereas tractional detachments are monitored until progression is quite definite. During the process, methazolamide is used to lower intraocular pressure. A combination of vitrectomy surgery and scleral buckling may be used in extreme cases of vitreous hemorrhage and traction (49). One potential complication is secondary glaucoma, if the sickle cells migrate into the anterior chamber and clog the trabecular meshwork in case of combined vitrectomy/lensectomy or vitrectomy in an aphakic patient (10).

In some cases, a preoperative blood transfusion may occur in order to lower the risk of intraoperative vaso-occlusion and ischemia by achieving the necessary level of hemoglobin.

In the future, a potential alternative treatment to vitrectomy may be intravitreal Bevacizumab injections, reported to produce neovascularisation regression; however studies are still in progress (50).

Medical alternative treatment includes haemostatic agents as aminocaproic acid or corticosteroids, that reduce the incidence of rebleeds in the setting of hyphema.

Conclusions

The importance of Sickle cell disease as public health concern is due to its associated significant morbidity and mortality. Although sickle cell trait is considered benign in a normal patient, its morbidity increases when hypoxia develops under conditions of stress, concomitant systemic diseases or trauma. Early detection and treatment are crucial. Future therapeutic treatment may involve the application of VLA-4 antagonists, which may help to delay the process of neovascularization and therefore improve the quality of life and survival potential of the patient.

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ISCHEMIC RETINOPATHIES	INFLAMMATORY DISEASE WITH POSSIBLE ISCHEMIA	OTHER
• Proliferative diabetic retinopathy	• Sarcoidosis	• *Incontinentia pigmenti*
• Branch retinal vein occlusion	• Retinal inflammatory vasculopaty	• Autosomic dominant vitreoretinochoroidopathy
• Ocular ischemic syndrome	• Medium uveitis	• Previous retinal detachment
• Hemoglobinopathies	• Eales disease	
• Retinopathy of prematurity	• Acute retinal necrosis	
• Eales disease		
• Familiar essudative vitreoretinopathy		
• Chronic myelogenous leukemia		
• Post scleral buckling ischemia		

Tabella 1: Differential diagnosis of the neovascularization of sickle cell retinopathy

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RETINOPATIA A CELLULE FALCIFORMI

L'occlusione di vasi di piccolo calibro all'interno dell'occhio, le neovascolarizzazioni retiniche e le loro conseguenze si verificano frequentemente in pazienti con anemia a cellule falciformi. Le lesioni neovascolari nascono al confine tra zone di retina perfusa e zone non perfuse. Nonostante alcune di esse vadano incontro a infarti spontanei, la maggior parte si accresce progressivamente portando a emorragie vitreali e distacco di retina. Lo sviluppo dei neovasi è stimolato dalla produzione di fattori di sviluppo vascolare, la cui immunoreattività è maggiore all'interno dei neovasi stessi rispetto alla retina adiacente e alle aree periferiche non perfuse. Tutte le lesioni possono essere osservate con oftalmoscopio e in angiografia con fluoresceina. E' necessaria la diagnosi differenziale con altre patologie retiniche di natura ischemica o infiammatoria. La gestione prevede il trattamento precoce con fotocoagulazione laser e crioterapia; la vitrectomia via pars plana e il cerchiaggio sclerale sono riservati ai casi in cui siano necessari.

Parole Chiave: Emoglobinopatie**,** Retina, Ischemia, Globuli rossi

CAPSULA EBURNEA, 5(4):15-22, 2010