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Ocular findings in homozygous sickle cell disease in Jos, Nigeria

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Summary

Ophthalmological examinations were performed in 78 homozygous sickle cell (Hb SS) patients, aged 4–42 years attending the sickle cell clinic of the Jos University Teaching Hospital, and the University Clinic, Jos, in Nigeria. Conjunctival signs present in about 77% of cases were observed in all ages and sexes. White without pressure present in 62.8% of the cases was the commonest retinal sign and in 56.3% of the cases was associated with peripheral retinal vessel disease. Salmon patches (6.4%), iridescent spots (10.3%), mottled brown areas (16.7%) and black sunbursts (7.7%) were seen as early as 10 years of age but showed an upward trend with age. Peripheral retinal vessel disease present in 52.5% of the cases was the second commonest retinal sign and with the exception of arteriolar occlusion showed no sex predilection, but an upward trend with age. Arterio-venous anastomosis (7.7%), vitreous haemorrhages and veils (3.8%) were the only severe proliferative signs noted. There were no cases of retinal neovascularization, retinal detachment or of angoid streaks, and the posterior poles were normal. Retinal signs were present as early as 8 years of age and showed an upward trend with age.

Résumé

Soixante-dix-huit cas de drepanocystoses SS âgés de 4 à 42 ans vus à Jos University Teaching Hospital et à 'University Health Centre' ont subit des examens ophthalmologiques complets. Les signes conjunctivaux présents dans 77% de cas ont été observés dans tous âges et sexes. Blancs sans pression, notés dans 62.8% de cas était le signe rétinien le plus fréquent et dans 56.3% de cas, était associé aux lésions de vaisseaux de la rétine périphérique. Les hémorragies saumonées (6.4%), les taches irisées (10.3%) les marbrures brunes (16.7%), et les échappées de soleil noires (7.7%) ont été notés dès l'âge de 10 ans mais grossissent avec l'âge. Les anomalies vasculaires périphériques présentes dans 52.5% de cas étaient en second lieu après blancs sans pressions et, à l'exception de l'occlusion artériolaire périphérique, n'avaient aucune prédilection pour sexe mais s'étend avec l'âge. Les anastomoses artérioveineuses (7.7%), les hémorragies du vitre et les voiles vitréens (3.8%) étaient les seuls signes prolifératifs notés. Il n'y avait pas de néovaisseaux de la rétine, de décollement de la rétine, de strie angoïdes, et les pôles postérieurs étaient normals. Les signes rétiniens se manifestaient dès l'âge de huit ans et grossissaient avec l'âge.

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Introduction

Approximately 27–30% of the 100 million Nigerians carry the sickle cell gene with over 1 million cases of homozygous sickle cell anaemia [1]. Sickle cell anaemia (Hb SS) is characterized by both haemolysis and a tendency for vessel obstruction and infarction. These changes lead to vascular occlusions in the spleen, lungs, kidneys, bones, CNS and other organs [2]. Also, several cases of vascular occlusions have been reported in the eye, especially affecting the conjunctiva [3,4] and the retina [5–7].

The conjunctival signs in sickle cell disease are more numerous on the bulbar conjunctiva and the inferior fornix and are present at all

ages. They are usually due to localized capillary occlusion by sickled cells and most of the lesions are thermolabile.

The small vessel obstruction characteristic of sickle cell disease mostly affects the retinal periphery although a few cases of posterior pole involvement have been reported [8]. Retinal lesions were divided into non-proliferative and proliferative [9]. Non-proliferative changes are usually non-progressive and rarely lead to reduced vision, while the proliferative retinopathies are usually progressive and lead to reduced visual acuity. Proliferative sickle retinopathy (PSR) is more common in sickle cell haemoglobin SC disease and S-thalassaemia, it is less common in sickle cell anaemia and only very few cases have been reported in haemoglobin AS carrier state [10–13].

Most of the work on the ocular complications of sickle cell disease was done in Jamaica [10–12], in the USA [7,9] and in France [6]. Little work has been done on this subject in Nigeria. This could be due to the facts that previously, most of the patients died in infancy and that most of the retinal lesions are peripheral and require special training and equipment to be recognized. This is the first report on the ocular complications in sickle cell anaemia patients seen in Jos, Nigeria.

Subjects and methods

All the sickle cell patients attending the sickle cell clinics at the Jos University Teaching Hospital (JUTH) and University Health Centre were referred to the Eye Department of the JUTH. Their ages ranged from 2 to 42 years. Children below the age of 3 years were excluded because of anticipated poor co-operation. Of the 88 patients referred to us, three aged between 3 and 4 years were excluded because of poor co-operation at fundoscopy. Seventy-eight of the patients included in the study had sickle cell haemoglobin SS disease while seven had haemoglobin SC disease. Of the 78 Hb SS disease patients, 41 were males and 37 were females.

Detailed ocular examinations included visual acuity assessment which was measured by the Snellen's test chart and/or the illiterate test. Intra-ocular pressure was measured in some cases by the applanation tonometer. All the patients were next dilated with gutt. phenylephrine 5% or 10% and gutt. tropicamide. Fundus examination was with the direct and indirect ophthalmoscopes, and the Goldman's three-mirror contact lens in some cases. Fluorescein angioscopy was done in some cases.

Diagnosis of haemoglobin abnormality was based on a positive sickling test and on haemoglobin electrophoresis, using cellulose acetate paper at pH 8.6. Other laboratory investigations included haemoglobin estimation, reticulocyte, platelet and white cell counts with differentials and red cell morphology. Fasting blood sugar was measured in some cases.

Results and discussion

The age and sex distribution of our patients is shown in Table 1. The conjunctival and retinal signs with their prevalence are listed in Table 2.

Symptoms

Only four of our patients presented with ocular symptoms. Three patients had visual acuity of below 6/36 which was due to posterior subcapsular cataract. The other patient presented with poor distant vision which was corrected with a minus 1.50 DS spectacle lens. All the other patients had either normal vision or mild ametropia.

Age and sex relationship

There was no relationship with age or sex in the incidence of conjunctival signs. Even though

Table 1. Age and sex distribution

Age (years)	Males	Females	Total
<9	12	14	26
10–19	15	16	31
20–29	9	7	16
30–39	4	0	4
40–49	1	—	1
Total	41	37	

Table 2. Conjunctival and retinal signs

Sign	No. of patients (n = 78)	Percentage
Conjunctival signs	60	76.9
Non-proliferative		
White without pressure	49	62.8
Mottled brown areas	13	16.7
Schisis cavity with iridescent spot	8	10.3
Black sunburst appearance	6	7.7
Salmon patches	55	6.4
Proliferative		
Arteriolar sheathing	16	20.5
Abnormal vascular dilatation and tortuosity	15	19.2
Arteriolar closure	10	12.8
Arterio-venous anastomosis	6	7.7
Retinal neovascularization (sea-fans)	—	—
Vitreous haemorrhage	3	0.8
Vitreous veils and fibrosis	1	1.3
Retinal detachment	—	—
Others	—	—

the non-proliferative signs were seen from 10 years and above, there appeared to be an upward trend with age (Mantel–Haenzsel χ^2 test for trend with age). There was no difference with sex. The proliferative signs were seen at all ages but again showing an upward trend with age. Only arteriolar occlusion seen in 80% of males showed any sex predilection. Figure 1 shows the age distribution of some retinal signs.

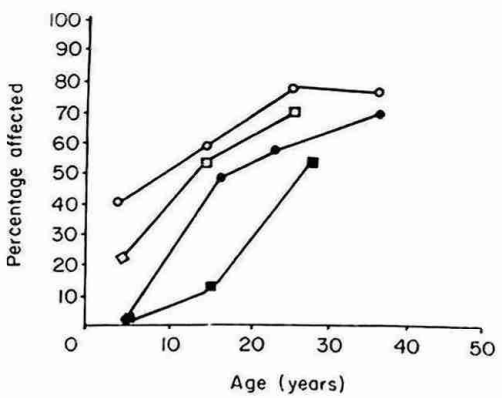

Fig. 1. Age distribution of some retinal signs. (○) White without pressure, (□) PRVD, (●) non-proliferative signs, (■) anastomosis and vitreous haemorrhages.

Multiple repeated vaso-occlusive episodes are believed responsible for the spectrum of symptoms, signs and histopathological findings present throughout the body in sickle cell diseases. Intravascular sickling promoted by conditions such as stasis is the single common factor leading to vascular occlusions and ischaemic necrosis of diverse tissues in sickle cell patients [2]. Even tissues or organs like the spleen, are vulnerable to vaso-occlusive phenomena in sickling. The conjunctiva and the retina are the main tissues affected in the eye.

Conjunctival signs

The conjunctival signs of sickle cell anaemia (Hb SS) are due to both excessive haemolysis and vasoconstriction, increased viscosity and localized sickling of red blood cells. The incidence of conjunctival signs has been variably reported. Kate-Sagokar *et al.* [14] reported an incidence of 26% while Serjeant *et al.* [15] reported an incidence as high as 98%. Nagpal *et al.* [16] in a report of 65 cases noted an incidence of 100% in 29 patients with Hb SS disease, 57.7% in 26 Hb SC patients and no sign in 10 Hb AS patients.

These conjunctival signs, which include ir-

regular venous dilatations, capillary micro-aneurysms, telangiectasic dilatations and comma-shaped vessels do not show any age or sex predilection. Most of these signs, especially capillary micro-aneurysms and venous dilatation, are thermolabile (disappear with heat) but reappear after instillation of vasoconstrictor drugs. Fink [4] postulated that the appearance of the capillary micro-aneurysms and venous dilatation with vasoconstrictor drops could represent a way of diagnosing sickle cell anaemia, since according to them, it neither occurs in sickle cell trait nor in normal people. For Swartz and Jampol [17] none of the conjunctival signs are pathognomonic of sickle cell anaemia as they have been reported in some cases with chronic granulocytic leukaemia. We think that even though the conjunctival signs should not be regarded pathognomonic of sickle cell disease, their presence should be a pointer to the existence of sickle cell disease.

Retinal changes

Opening and closing of retinal vessels by plugs of deoxygenated erythrocytes occurs in patients with sickling haemoglobinopathies [5,18,19]. These changes may or may not be associated with retinal ischaemia or infarction depending on such factors as location, duration and size of obstruction and the presence or absence of collateral blood flow. There appear to be three types of retinal vascular occlusions in sickle cell disease: transient occlusion without noteworthy retinal ischaemia, transient occlusion which later reperfuses but leaves behind an infarcted retina, and permanent vascular occlusion with no reperfusion of the infarcted capillary bed [20]. Thus depending on which type of occlusion occurs and on its location, size and duration, two types of retinal lesions can occur: non-proliferative and proliferative.

White without pressure was seen in 62.8% of our patients and constitutes the commonest retinal lesions. They consist of hazy pallor of the peripheral retinal surface and either occur in localized patches or affect the whole periphery with or without vitreous condensation. Condon and Serjeant [10,12] found whitening of the retinal periphery in 93.4% of patients with Hb SS disease and 82.4% with Hb SC disease. About 72.9% of their patients showed associated peripheral retinal diseases. In our series only 56.3% of the patients with white without pressure showed obvious peripheral vessel disease. The cause of whitening of the retinal peripheral has been a subject of controversy but most authors, including Goldberg [9], attribute it to retinal hypoxia that gives rise to retinal oedema.

Salmon patches, i.e. the typical salmon fish colour of retinal haemorrhages, were present in 6.4% of our patients. These salmon patches may be round or oval in shape, bright red or yellowish white, and are seen in the mild or far periphery of the retina. The cause of their peculiar colour is not known. Salmon patches are almost always pathognomonic of sickle cell disease. They are rarely seen in other occlusive retinal diseases [21]. They can disappear leaving atrophic and thin retina or they can give rise to silvery-yellow iridescent spots and retinal schisis cavities.

Iridescent spots are copper-coloured glistening deposits that occur at the site of previous intraretinal haemorrhages. They usually occur at the centre or close to mottled brown areas. We noted this sign in 10.3% of the patients.

Mottled brown areas were seen in 16.7% of our cases, making it the second commonest non-proliferative retinal sign. They are usually oval or circular, one to three disc diameters in size with an uneven mottled brown appearance in which smaller irregular areas of lighter colour are interspersed. These brown areas may be due to haemosiderin deposits in the deeper layer of the retina as a result of intraretinal haemorrhages. They represent an intermediate state between retinal haemorrhages and black sunbursts.

Retinal black sunbursts were first described by Welch and Goldberg [7] and are circular black chorio-retinal scars with stellata or spiculate borders, commonly found in the peripheral fundi of sickle cell patients. As they usually occur in the fundus periphery, they do not interfere with vision. Condon and Serjeant [10–12] reported their incidence as 41% in sickle cell Hb SC disease, 35% in Hb SS disease and 20% in S-thalassaemia. Only 7.7% of patients in our study had black sunbursts. This is far below the 35% reported by Condon and Serjeant in homozygous sickle cell disease patients seen in Jamaica [12]. The reason for this low incidence in our patients is not clear,

but the features of sickle cell disease in Nigeria and Jamaica are not quite the same [22]. Black sunbursts usually arise from the effect of blood and its breakdown products that irritate the pigmentary epithelial cells and cause them to proliferate. Chorio-retinal scars from toxoplasmosis and syphilis are a very important differential diagnosis.

Proliferative changes

Proliferative retinopathy could be divided into mild and severe. The mild cases could also be grouped as peripheral retinal vessel diseases which are precursors to the more severe proliferative sickle retinopathy (PSR) and its sequelae.

Peripheral vascular disease includes the very early vascular changes of the peripheral retinal vasculature and stage I of the classical Goldberg's five-stage classification of PSR. These peripheral retinal vascular diseases (PRVD) include arteriolar sheathing, abnormal venous dilatation, vascular tortuosity and arteriolar occlusion. Condon and Serjeant [12] reported 93.4% incidence among homozygous sickle cell disease patients in Jamaica. In our series, only 52.5% of the patients showed peripheral retinal vascular disease. These signs were seen as early as in an 8 year old, but they became progressively more common with advancing age.

The five-stage classification of PSR by Goldberg [9] is still the most accepted. Stage I, which represents arteriolar occlusion, was present in 12.8% of our cases. Stage II or arterio-venous (A-V) anastomosis was present in 7.7% of the cases. These A-V anastomoses are usually situated between the post-equatorial vascularized retina and pre-equatorial ischaemic retina. The release of vasoproliferative factors from the pre-equatorial hypoxic retina induces the formation of fragile capillary buds from the venous segment of the A-V anastomosis. These capillary buds with acquired fibrous tissue proliferation represent stage III, or the stage of sea-fan neovascularization. They are so called because the neovascular and fibrous growths often take a fan-shaped form that resembles the marine sea-fan *Georgiona flabellum*. Sea-fans are highly characteristic but not pathognomonic for PSR for they occur in other disease including Eales' disease, sarcoidosis, chronic leukaemia, rheumatic fever and others [23]. Sea-fan neovascularization is most characteristic of sickle cell haemoglobin Hb SC disease and sickle cell B-thalassaemia. It is less common in homozygous patients with sickle cell anaemia and very rarely seen in the sickle cell (AS) carrier stage. In a non-selected group, Goldberg found sea-fan neovascularization in 32.8% of Hb SC patients, 14% in S thalassaemia and in 2.6% of Hb SS individuals [23]. We did not observe any case among the 78 patients with Hb SS disease.

Vitreous haemorrhages represent stage IV. They could be local or diffuse, minor or massive, but visual symptoms occur only when blood diffuses into the visual axis. The haemorrhages arise either from the sea-fan during posterior vitreous detachment or from extension from subretinal, intraretinal or preretinal haemorrhages. We noted vitreous haemorrhages in three of the 78 patients studied, one of whom had vitreous fibrosis and veils indicating previous vitreous haemorrhages. As there was no retinal neovascularization in our patients the vitreous haemorrhages could only have arisen by diffusion from intraretinal haemorrhages. The ultimate effect of the repetitive vitreous haemorrhages is vitreous condensation, fibrosis and formation of tractional bands. Constant vitreous traction to adjacent and remote portions of the retina could cause retinal tears or holes to develop. The net result is rhegmatogenous retinal detachment with significant tractional components. These detachments may remain localized but usually become total and are particularly difficult to correct surgically [24]. We did not observe any case in our study group although we noted it in two of seven Hb SC patients in a parallel study group.

In conclusion we wish to highlight the low incidence of the conjunctival and retinal signs in our study group, compared to those of Condon and Serjeant [10–12] among Jamaicans. As the retinal signs show an upward trend with age and it is well known that Jamaican sicklers have a longer lifespan than Nigerians, it could be that we were dealing with patients of a younger age group.

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