Ocular findings in children with severe clinical symptoms of homozygous sickle cell anaemia in Kaduna, Nigeria

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Summary

Background: **Sight-threatening retinopathy in Sickle Cell Disease is thought to be due mainly to vasoocclusion. Yet it is reportedly rarely found in children with Haemoglobin SS, (who most often suffer from vasoocclusion). However, earlier reports included patients with a wide range of clinical severity.**

Aim: **To document ocular pathology in children with Haemoglobin SS with severe clinical disease.**

Methods: **Thirty-seven children with severe clinical disease (at least 3 vaso-occlusive episodes in one year) had detailed ocular examinations over a one-year period.**

Results: **No child (aged 3 to 13 years) had ocular symptoms. Visual acuity was abnormal in one child. Retinal pathology was found only in patients over 8 years. Neovascularization was observed in 3 eyes of 2 patients both of whom had higher than average irreversibly sickled cell counts and haemoglobin levels. Retinal and choroidal infarcts were found in 11 and 2 eyes respectively; sunburst lesions and salmon patch haemorrhages in 5 eyes each. Changes observed over the one-year period in the 32 survivors, were photocoagulation scars in one eye of a child who had undergone laser therapy and resolution of the salmon patch haemorrhages.**

Conclusion: **Despite lack of visual symptoms, young children with haemoglobin SS with severe clinical symptoms can develop sight-threatening retinopathy. The possible role of autoinfarction in the causation of these lesions is discussed. Our study shows that routine yearly ophthalmological examinations are essential for children over 8 years.**

Key-words: ***Sickle, Cell, Disease, Retinopathy, Eye.***

Résumé

Plan: On croit que la retinographie menacant la vue dans la maladie "Sickle Cell" est cause par la vaso-occlusion. Malgré cela, il aurait dit qu'elle se trouve rarement dans les enfants possedant la Hemoglobine SS, (qui souffrent souvent de la vaso-occlusion). Pourtant, les premiers rapports incluent les malades avec une vaste étendue de sévérité clinique.

But: Documenter la pathologie oculaire dans les enfants possedant la Hemoglobine SS avec une maladie clinique sévère.

Procede: Trente-sept enfants avec la maladie clinique sévère (ayant au moins 3 episodes vaso-oclusives en un an) avaient eu des examen oculaires detailes dans une periode d'un an.

Résultats: Pas d'enfant (âge de 3 a 13 ans) avait des symptomes oculaires. Il y avait une acuite visuelle anormale dans un des enfants. Une pathologie retinale était observee que dans chez les enfants malades ayant plus de 8 ans. Une Neovascularisation était observee dans 3 yeux de 2 malades qui avaient tous les deux, un degre en plus de moyen de numerations *Sickle cell* irreversibles et des niveaux hemoglobins. On avait trouve des infarctus retinaux et choroids dans 11 et 2 yeux respectivement; des lesions echappees et des hemorrhagies de truites saumonees dans 5 yeux chacun. Les changements observes lors de la periode d'un an dans les 32 survivants, étaient la photocoagulation dans un oeil d'un enfant qui a subit une therapie Laser et une resolution des hemorrhagies de truites saumonees.

Conclusion: Malgre le manque de symptomes visuals, les jeunes enfants avec la hemoglobine SS possedant des symptoms cliniques severes peuvent developper la retinographie menacant la vision. Le role possible de l'auto-infarcation dans la causation de ces Lesions est discute. Notre recherché montre que les examens ophthalmologiques annuels reguliers, sont essentiels pour les enfants qui ont plus de 8 ans.

Introduction

Sickle Cell Disease (SCD) is the most common genetic abnormality that occurs in black Africa.[1] In Nigeria at least 100,000 children are born with the disease every year. Ocular morbidity is a well recognised complication of the condition and can affect any structure of the eye.[2] Vision-threatening problems are most commonly due to peripheral retinal neovascularization.[2] This occurs as a result of microvascular occlusion, leading to ischaemia,[3] which then results in the formation of new vessels (neovascularization). These new vessels develop at the border of vascular and avascular regions and proliferate (proliferative sickle cell retinopathy - PSR).[3,4] The significance of PSR lies in the fact that the new vessels are fragile, and leak protein and red blood cells resulting in vitreous haemorrhage, retinal traction, detachment and blindness.[2,4] This leakage is shown by intravenous administered flourescein. Visual loss occurs more commonly in patients with Hb Electrophoretic pattern SC or Hb SB^+ thalassaemia than in those with Hb SS.[5,6] Retinopathy is rarely said to occur before the age of 15years in children with HbSS.[7,8] However Abiose[9] reported potential sight threatening retinopathy (i.e. peripheral arteriolar occlusion, neovascularization) in 6% of Hb SS children under the age of 12years. She noted that severe vascular disease could occur even in young children. As progression of retinal changes can be halted if detected and treated early,[2,6,10] it would appear best to routinely examine all children with Hb SS at regular intervals. As most visual loss is as a result of microvascular occlusion, it would seem logical to assume that patients with SCD who suffer from repeated episodes of vasoocclusion might be most vulnerable to ocular pathology. Yet previous studies suggest that while the most systemic complications are observed in patients with Hb SS, the most severe ocular

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features occur in patients with Hb SC.[3,6] However these reports included children with a wide range of clinical severity from mild to severe. The situation in patients who suffer from repeated severe vasoocclusive crises is unclear. The study thus set out to document ocular changes in children with Hb SS with severe clinical symptoms as defined by 3 severe vasoocclusive crises in one year.

Materials and methods

The study was a prospective one involving children with SCD seen in the Paediatric department of the Ahmadu Bello University Teaching Hospital who were referred to the ophthalmic department of the same hospital for ophthalmological assessment.

The inclusion criteria were as follows: Children aged less than 15 years, with Haemoglobin pattern of SS, as confirmed by Hb electrophoresis, and who had experienced at least 3 painful or vaso-occlusive crises in the previous year. A painful or vaso-occlusive crisis was defined as an acute painful event requiring treatment at a healthcare facility or at home with either parenteral or equianalgesic dose of oral non-steroidal anti-inflammatory drugs or narcotics. It included episodes of bone pains, abdominal pains, acute chest syndrome, splenic or hepatic sequestration or priapism, haematuria, and cerebral vascular accident due to vasoocclusion.

All children had a detailed ocular examination as follows: Assessment of visual acuity was done using Snellen's chart. Anterior segment structures viz conjunctiva, cornea and iris were examined using a pen torch and in more detail with a slit lamp. Both eyes of the patient were dilated using cyclopentolate 0.5% and 5% phenylephedrine for detailed fundal examination. Both direct and indirect ophthalmoscopy were then carried out to search for lesions in the posterior segment.

Special care was taken in examining the periphery of the retina. There were no facilities for flourescein angiography or fundal photographs. The same procedures were repeated at 6 months and 1 year. Haematological investigations were also done at the beginning of the study, and at six months and 1 year. They consisted of a full blood count and differential, reticulocyte and irreversibly sickled cell counts. There were no facilities for estimation of Haemoglobin F levels.

Result

A total of 37 patients (74eyes) were initially enrolled into the study. Their ages ranged from 3 to 13 years and they were made up of 20 (54%) male and 17 (46%) female (Table 1).

Symptoms

There were no ocular symptoms.

Visual acuity (Table 2)

This was carried out in 60 out of 74 eyes because 7 patients were too young to cooperate. Out of the 60 eyes examined, 55(91.6%) had a visual acuity of 6/6 or better:4 eyes had visual acuity of between 6/9 to 6/18. Only one eye had poor visual acuity (below 6/18).

Anterior segment lesions

Abnormal corkscrew and comma shaped vessels situated

Table 1 Age/Sex of patients

Age (Years)	Male	Female	Total Number	% Total
3 - 7	8	6	14	37.8
8 - 12	10	6	16	43.3
>13	2	5	7	18.9
Total	20	17	37	100

Table 2 Unaided visual acuity in sixty eyes examined

Visual acuity	No. of eyes	% of total
6/5 - 6/6	55	91.66
6/9 - 6/18	4	6.66
Less than 6/18	1	1.68
Total	60	100

Note: Visual acuity could not be done in 7 patients (14 eyes)

Table 3 Age/Sex distribution of retinal lesions

Age (Years)	Total No. of patients	Retinal Lesions			
		Male	Female	No. affected	% total
3 - 7	14	0	0	0	0
8 - 12	16	5	3	8	50%
>13	7	1	3	4	57%
Total	37	6	6	12	32.4%

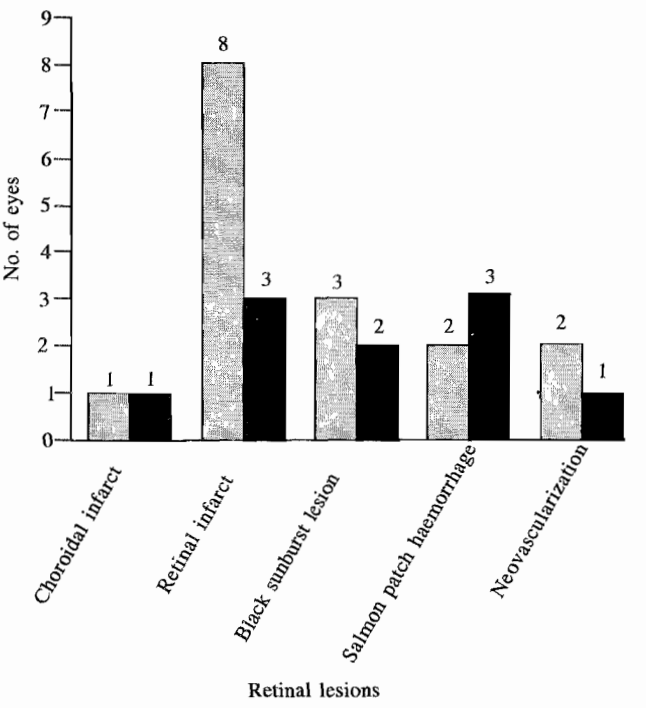

Fig. 1 ***Eye laterality and distribution of posterior segment lesions***

mainly in the inferior conjunctiva were found in 70.3% of the patients. This was the only anterior segment anomaly noted.

Posterior segment lesions

Retina lesions (Table 3, Figure 1)

Retinal lesions were found in 12 (32.4%) of the children, all of whom were above 8 years of age. There was no sex differential. The most common lesion was retinal infarcts seen in 11eyes (14.9%), seen mainly in the right eye of patients. These infarcts were small whitish circumscribed areas of the retina mainly situated in the periphery, which did not interfere with vision. Other infarcts seen were numerous discrete circular chorioid infarcts seen in both eyes of one patient. Neovascularization was observed in 3 eyes of 2 patients. One was a 13-year-old female who had a localized cluster of abnormal new vessels in the left eye inferior temporally. The other was an 8-year-old boy who had evidence of abnormal new vessels in the retinal periphery especially in the temporal quadrants of both eyes. Since flourescein angiography was not carried out, it was impossible to confirm if leakage of dye into the vitreous occurred in these patients. Pigmented chorioretinal scars (Sunburst lesions) and Salmon patch haemorrhages were seen in 5 eyes each.

Vascular abnormalities

Abnormal tortuosity of the major vessels of varying degrees was seen at the disc and posterior pole in 54% of patients. Dilatation of choroidal vessels was also noted in the retinal periphery of 65% of the patients.

Haematological investigations

The average haemoglobin level for the patients was 6.9 g/dl (range 5 - 9.5g/dl). The 2 patients with neovascularization had higher than average haemoglobin levels of 7.6 and 9.6g/dl. They also had higher than average irreversibly Sickled Cells (ISC). The average ISC of the patients was 153/100 (range 1-455/100) while that of the 2 patients was 213 and 223/100.

One year review

After 1 year, 32 patients (64 eyes) were re-examined as 4 patients died and 1 was lost to follow up. The findings were basically unchanged except for the 8-year-old boy with neovascularization. He had received laser therapy in the United Kingdom. He had laser burns in the left eye but his visual acuity (previously 6/18) was noted to have improved to 6/12. This was thought to be due to correction of his astigmatic refractive error, (unaided Va of 6/12) with glasses (aided Va 6/6). The other patient who had neovascularization still retained normal vision. The salmon patch haemorrhages seen resolved in the five eyes over the one-year period.

Discussion

Children in this study were selected on the severity of clinical disease and not on ocular symptoms. However despite the fact that none of them had any ocular symptoms, various ocular signs were found in them. This included retinopathy in 32.4%, abnormal conjunctival vessels in 70.3%, and retinal vessel tortuosity in 54% of cases. It should be noted that retinopathy was not discovered in any patient less than 8 years but potentially sight-threatening retinopathy (neovascularization) was found in 3(4.0%) of the children over 8 years. The study was limited in that it was not possible to perform flourescein angiographic studies on these children, so it was not possible to determine if these children leaked flourescein into the vitreous. However, though nearly all structures in the eye can be affected by SCD, vision-threatening problems are usually due to retinal neovascularization. This is because the new vessels are fragile, leak protein and red blood cells producing vitreous haemorrhage, retinal traction, detachment and blindness.[3,4]

The prevalence of neovascularization in people with SC and SB+ thalassaemia, which have milder systemic signs of SCD, is higher than in those with HbSS.[2,5] HbSC causes hypoxia in the retina due to partial blockage of arterioles while HbSS causes infarction due to total blockage of arterioles. The hypoxia in HbSC is believed to induce a vasoproliferative substance in the retina, which causes the development of abnormal new vessels, which does not often occur in HbSS.[11] In addition autoinfarction can occur and can lead to infarction of new vessels.[2,3,12] Autoinfarction is common in both SS and SC disease, but is consistently more frequent in SS.[12] If this postulate were true, then patients with SS would be expected to have a high prevalence of retinal infarction but low incidence of neovascularization.[2] In this study, the most common finding in the posterior segment was that of retinal infarcts. Only 2(5.4%) of the children were found to have peripheral neovascularization. The relatively high incidence of retinal infarcts and low incidence of neovascularization tends to lend credence to the theory of autoinfarction. However the finding of peripheral neovascularization in 5% of the children is surprisingly high when compared with other studies. Most series report that peripheral neovascularization rarely occurs before 13 years.[7,8,13] Abiose[9] in her study of 102 children of similar age and racial background observed neovascularization in only one case (an 8 year old child) i.e. 1% of her patients. She did not report any retinal infarcts. Talbot et al did not observe any neovascularization in 59 children with Hb SS disease though 14% of them had signs of peripheral vascular closure and 37% retinal patches.[7] However in their study, all the children were less than 8 years. These differences might be due to the method of patient selection (this study was limited to those with severe vasoocclusion) whereas in both Talbot and Abiose's studies children with various grades of clinical severity were included. Kent et al[11] in their study of 50 patients did not however find any correlation between the grade of retinopathy and age or systemic complications.

One year after the initial examination, most of the main findings of the children remained unchanged, and neither of the 2 children with peripheral neovascularization had developed worsening signs. This was partly due to the fact that one of the children had received treatment with laser therapy with ablation of the new vessels. However the other child who received no treatment still retained good vision. Not all patients with PSR develop blindness[2,6] but the chances of vision being affected increase with time, as once established, progression of PSR is common particularly in

young patients.[11, 14] Other researchers in trying to identify patients most likely to develop PSR found those that had a high Hb (greater than 9g/dl) appeared to constitute a high-risk group for PSR in males.[15] Retinal vessel closure was significantly correlated with low total haemoglobin and high HbF and irreversible sickled counts in SS disease.[16] Both children with neovascularization in this study had higher than average haemoglobin levels and irreversible sickled counts but the numbers are too small to make any definite conclusions. Other studies however found no correlation between retionopathy and haemotological parameters.[11]

The other ocular changes observed in the children do not usually cause visual loss. Haemorrhages (Salmon patch and sunburst lesions) were found in 6.8% eyes each. They usually resolve with few sequelae. Tortuosity of major retinal vessels is reported in many patients with SS disease as well as in a variety of other conditions. Other studies report prevalence of between 11 - 47%.[17,18] In this study it was seen in just over half of the children. The mechanism by which it develops is obscure.[2] In the anterior segment the only abnormal sign found was the 'comma shaped' conjunctival vessels. This is a common sign in patients with SCD and is found in 32 - 80%[9,12,19] of patients. It is thought to be due to intravascular sludging of sickled red blood cells but does not generally cause significant vision loss.[2]

Thus in conclusion in this study, the most significant findings were those of neovascularization in 2 patients despite lack of ocular symptoms. It is likely that the number of children with vision threatening signs will increase with time as occurred in other studies. As early detection and treatment of these lesions are feasible, there is enough justification for prospective ophthalmic examination of all SCD patients as proposed by Serjeant.[2] However because of the heavy patient load in Africa, this is not likely to be feasible. Other workers have advocated routine yearly examination of Hb SS patients over the age of 20years.[5] But as this study has shown, significant retinal vessel disease can occur in children as young as 8 years. The study suggests that this may occur more commonly in patients with severe homozygous SCD but further research and case control studies would be needed to confirm this.

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