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When should children and young adults with sickle cell disease be referred for eye assessment?

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Summary

Children and young adults who suffer from sickle cell disease (SCD) are at risk of blindness from retinopathy and other complications. The incidence of proliferative retinopathy in SCD patients varies from 5 to10% depending on the genotype, being commoner in SC than SS and S-thal. 'Sudden' blinding sequelae such as vitreous haemmorrhage and tractional retinal detachment can eventuate from vasculo-proliferative retinal lesions, known as sea fans, in otherwise 'quiet' eyes. This risk can be minimised considerably if the lesions are detected in a timely fashion and treated, usually with laser photocoagulation and possibly with cryotherapy. This communication aims, by a review of relevant literature and through our original data, to highlight a time frame for the development of proliferative sickle retinopathy to enable paediatricians decide on an appropriate time of referral for ophthalmic assessment. Ninety patients with SCD (88 SS, 2 SC) aged 5-36 years were examined for anterior and posterior ocular signs of SCD using dilated binocular indirect ophthalmoscopy. Other relevant literature was reviewed. Twenty-four percent of these patients had some form of SCD related posterior pathology, 5.6% of which was preproliferative or proliferative. This included a 14-year-old SS patient with arterio-venous anastomosis. The literature reveals that patients begin to exhibit evidence of proliferative retinopathy from about the age of 10 and the frequency tends to increase with age. However, though rare, vitreous haemmorhage has been known to occur below the age of 20. Children with SCD should, from about the age of ten, be referred for at least biennial dilated binocular indirect ophthalmoscopy preferably with fluorescein angiography if such facilities are available, so that neovascular lesions can be treated before blinding sequelae occur. From the age of 20, the frequency of eye examination should increase to yearly. Antisickling remedies, such as NIPRISAN® may be beneficial in prophylaxis.

Keywords: *Sickle cell disease, retinopathy, vitreous haemmorhage, photocoagulation.*

Résumé

Les enfants et les Jeunes adults drepanocitaire courent le risqué d'etre aveugle de la retinopathic et des autres complications. L'incidence de retinopathic chez les drepanocitaires vari de 5 a 10% dsependant du genotype, leci etant plus frequent chez les SC que les SS et S-thal. Les sequels soudaine aveugle a savoir, haemorrhagie vitreuse detachement re international paivent eventuer des lesions vasculo-proliferative retinale qui sont les suivant; "Sea fans" antrement dit "quiet" eye le risqué peut etre minimiser considerablement if les lesions sont detecteres a temps et traitees, le plus souvent avec le laser photacoagulation et ai possible avec la cryotherapy. L'objectif de Cette communication par une nevue literaire et par les donnes originate est de meltre en lumiece une structure de temps pour les development l'un moyen de detecter la retinopathic depanocitaire afin de paettre aux pediatricians decider sur le temps appropries pour referrer les molades four des examens ophthamologiques. 90 patients drepanocitaire (88 SS, 2 SC) ages de5 a 36 ans avaient ete examines pour les signes oculaire posterieur et anterieur avec l'ophthalmoscopic binoculaire indirect delate'. Les autre literature clevantes avaient ete revues. 24% de ses patients avaient des fommes drepanocitaire elie a la pathologie posterieure, 5.6% parmi ceux-a etaient pre-proliferative on proliferative. Ceci compris un patient SS de 14 ans avec une anastomose atriaveneux. La literature montre que les patients ont commence a exhiber une evidence de retinopthaies proliferative partir de 10 ans et la frequence augmente avec e'age. Parcontre mais rarement, e'haemorrhagie vitreuse a'de connue affectant les jeuns de moin de 20 ans. Les enfants drepanocitaire doivent a partir de 10 ans etre referred pour l'ophthalmoscope Binoculaire indirect dilate au moins 2 fois par an de preferable avec la fluorescein angiographique si il yen a de tele facilite a fin que les lesions neovasculaire sarent traits avant que cela ne aveugle. A partir de l'age de 20 ans la frequence de l'examen de e'aiile loit sugment a une fois paran. Les remeds antidrepanocitaires comme le NIPRISAN® pourrait etre utile pour le prohylaxie on prevention.

Introduction

Sickle cell disease (SCD) is recognised as a significant cause of blindness and ocular morbidity [1]. The incidence of proliferative retinopathy tends to vary from 5 to 10% of SCD patients. Early detection of lesions allows prompt treatment and prevention of blinding sequelae. The purpose of this communication is to highlight a time frame for the natural course of sickle cell retinopathy to enable doctors engaged in the care of SCD patients decide on appropriate time and criteria for referral to ophthalmologists. This will be done with special reference to our study of 90 Nigerians with SCD and with regard to other published material on the subject.

The term SCD is here used to refer to patients with haemoglobin genotypes SS, SC and Sthal. Retinopathy occurs more commonly in SC disease even though the general clinical course of SS is more severe [2]. Retinopathy has also been reported to occur in AS and AC, [3, 4] especially where other risk factors for retinopathy exist such as diabetes and hypertension.

Causes of blindness in SCD include vitreous haemmorhage, tractional detachment of the retina, ischaemic maculopathy (5), central retinal artery occlusion [6] and cortical blindness [7].

Otherwise asymptomatic patients have been known to present with vitreous haemmorrhage [8] and tractional retinal detachment generally eventuates from the organisation of vitreous haemmorrhage. These two are the more commonly reported causes of blindness in SCD. [9]. The most commonly applied treatment modality is laser photocoagulation of proliferative lesions ('sea fan' neovascularisation). There are three ways in which this is applied: to the feeder vessel, in form of scattered 360° peripheral laser burns and in form of local scatter photoco-

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agulation to the region of the neo-vascular net. It is also possible to use cryotherapy especially where facilities for laser are unavailable. The role of antisickling remedies in the treatment and prevention of eye lesions is still being investigated.

Photocoagulation is applied either externally through a slit lamp or at the time of vitrectomy, i.e. endolaser. Transcleral application of diode laser has also been advocated [10]. It is of course preferable to treat the friable sea fans before vitreous haemmorrhage occurs. When vitreous haemmorrhage does occur, most practitioners will wait for a period of six months to allow for spontaneous clearance before attempting vitrectomy. If tractional retinal detachment occurs consequent upon the vitreous haemmorrhage, the surgical procedure becomes much more complicated and chances of meaningful visual recovery diminish, especially if the macula is involved in the detachment. The need for timely referral of children and young adults at risk cannot therefore be over-emphasised.

Anterior segment changes such as jaundice, iris atrophy and comma shaped/corkscrew vessel formation are of interest but do not cause visual loss.

Patients and method

Ocular findings in 90 patients with electrophoreticaly confirmed SS (88) or SC (2) disease is described. The patients are black Nigerians drawn mainly from Abuja City and its environs. They form subjects in a phase IIb pivot double-blind crossover trial of the phytomedicinal antisickling preparation, NIPRISAN. Results of the trial will be published subsequently. They were examined for anterior segment signs and posterior segment ocular signs of sickle cell disease after dilatation, using binocular indirect ophthalmoscopy. Fluorescein angiography was not done. Data was entered into Borland D-Base 5.0 for windows and analysed using EPI info version 5.01a (1991).

Results

Male -Female distribution within the study population was 47/43. The age ranged between 5 and 36 averaging 15.3yrs with mode in the 10-14 group. Table 1 shows the age and sex distribution of the patients. Eighty-seven of the patients had a visual acuity better than or equal to 6/9 in either eye. One had NPL (No Perception of Light) vision associated with an eviscerated socket consequent upon an earlier injury.

Table 1. Age and sex characteristics of study population.

Age group	Male	Female	Total
5-9	2	2	4
10-14	19	24	43
15-19	15	15	30
20-24	5	1	6
25-29	3	1	4
30-34	2	0	2
35-40	1	0	1
Total	47	43	90

Anterior segment finding

Corkscrew or comma shaped vessels was seen in 51 individuals characteristically bilaterally except in three cases. Twenty-nine subjects had clinically evident jaundice. Nineteen patients had both of these signs. Put together, these signs appeared to be commoner in the younger age groups but the trend did not achieve statistical significance P = 0.37. (Fig. 1).

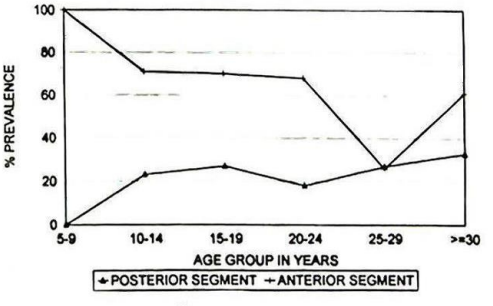
Posterior segment findings:

Some form of SCD related posterior pathology was found in 22 subjects (24%). Nineteen of these had NPSR (None Proliferative Sickle Retinopathy) and 5 (5.6%) had PSR (Proliferative Sickle Retinopathy) while 2 had both. The frequency of NPSR signs is as follows: schisis cavities/iridescent spots 13 (14.4%); Black sunburst lesions 6, vitreous fibrosis 3; salmon patch 2; pre-retinal haemmorhage 1. It should be noted that some of the patients had multiple pathology. All the patients with vitreous fibrosis were male, aged 14, 17 and 29, respectively. The 14-year-old had a co-existing A-V anastomosis in the affected eye and the 29-year-old also had vascular occlusion. These two cases therefore had both proliferative and non-proliferative signs. The frequency of PSR signs is as follows: vascular occlusion 3; Arterio-Venous anastomosis 2; sea fan neovascularisation 1. These PSR lesions were bilateral in two cases and unilateral in three. The youngest patient with PSR was 14, the others being 17,18, 25 and 29 years of age. Sea fan neovascularisation, which is the most advanced PSR lesion seen in this series, occurred in a 25-year-old lady.

Maculopathy: Ten eyes of six individuals had clinically apparent maculopathy, although they may not be attributable to SCD. This was associated with reduced visual acuity (6/24) in one eye.

Eighty-one percentage of all 90 subjects had some form of eye finding related to SCD. Twelve patients had both posterior and anterior pathology, 51 had only anterior pathology and 11 had only posterior pathology. Anterior signs tended to be commoner in the younger age groups, while posterior signs tended to be commoner in the older age groups. These trends did not however achieve statistical significance. (Fig.).

FIG 1: AGE SPECIFIC RATES (%) OF ANTERIOR AND POSTERIOR OCULAR PATHOLOGY IN SUBJECTS WITH SICKLE CELL DISEASE



Discussion

The detection of posterior ocular pathology in SCD is not easy because most of the lesions are peripheral and can only be seen after full dilatation of the pupils and with Binocular Indirect ophthalmoscopy. The use of Fluorescein angiography greatly enhances this process. However it must be noted that very few centers have this facility in sub-Saharan Africa. The average busy doctor cannot be reasonably expected to have the time or equipment necessary for this. The use of Snellen acuity and the direct ophthalmoscope, which facilities may be available to some doctor practitioners, will not detect the presence of these

lesions, with the possible exception of ischaemic maculopathies. To what extent did anterior segment sign indicate presence of posterior signs? Twelove of the 63 subjects with anterior sign had posterior sign (about 1 in 5) while about half of those with posterior sign had anterior sign.

A quiet anterior segment with no SCD related sign therefore often belied the presence of sight threatening pathology posteriorly because almost half of the subjects with retinal lesions showed no sign of anterior change. Contrarily, the presence of anterior lesions does not necessarily point to posterior pathology: only one in five subjects with anterior signs had posterior lesions. For these reasons, 'sudden' visual loss in SCD patients is not uncommon, usually from vitreous haemmorrhage [11] which sometimes, though infrequently, occurs before the age of twenty especially with SC disease. 'Sudden' visual loss can also occur less often from tractional retinal detachment, central retinal artery occlusion and cerebral infarction. For the aforementioned reasons therefore it becomes desirable for patients to be referred for ophthalmic evaluation at an appropriate time.

What constitutes the 'appropriate time?' In our study, the youngest patient with evidence of PSR in form of an Arteriovenous anastomosis was a 14-year-old boy, while sea fan neovascularisation was seen in a 25-year-old female. In the literature, sea fan neovascularisation has been noted in an 8-year-old girl with SC genotype [12] and in a 13-year-old [13]. In fact according to one study, 90% of children with SS and SC genotypes have vessel closure detectable by fluorescein angiography by age 12 [12]. In the study of sickle cell retinopathy in children under the age of 20, Kimmel *et al* [13] documented PSR using the technique of fluorescein angiography in 8% of males and 3% of females. Fox *et al.* [14], while examining risk factors for proliferative retinopathy, found that the first cases of PSR were observed in patients in their late teens, the incidence rate increasing in patients who were 25 years and older. A review of the literature tends to indicate that intervention is necessary and effective. A ten-year assessment of 120 patients with homozygous sickle cell anemia and 222 patients with SC disease demonstrated visual acuity loss (20/30 or less) in 10% of untreated eyes [15]. Also, 80% of eyes with untreated PSR had persistent sea fans after 10yrs. [16]. Therefore, treatment of PSR is necessary to prevent vision threatening complications, including vitreous haemmorhage and retinal detachment. [17]. From about the age of ten therefore, it is desirable that children with SCD should have an ophthalmic consult with at least dilated binocular indirect ophthalmoscopy and possibly Fluorescein angiography if the facilities are available. This would enable prophylactic measures or early therapeutic measures to be instituted before sight threatening sequelae result. This can be carried out biennially until the age of twenty when annual assessment may be instituted.

The role of antisickling remedies such as NIPRISAN® which is under current investigation, in the management of ocular disease from sickle cell anemia, has not been properly delineated, although our early results tend to indicate that it may reduce the incidence of posterior segment changes by about 50%.

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