Ocular Manifestations of Sickle-cell Disease at the Korle-bu Teaching Hospital, Accra, Ghana.

A dissertation submitted in partial fulfillment of the requirements for a master of medicine degree in ophthalmology.

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Principal Investigator

Dr. Alfred Osafo- Kwaako BSc MBChB. (UGMS, Ghana)
Registrar, Dept. of Ophthalmology, University of Nairobi.

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DECLARATION

This dissertation is my original work, and has not been presented for a degree at any other university.

Signed.........Osafo Kwaako AO..........................

Date ....01 / 09 / 08.........................

Dr. Alfred Oduro Osafo- Kwaako.

APPROVAL.

This thesis has been submitted for examination with our approval as university supervisors.

1. DR. KAHAKI KIMANI,   MBCHB, MMED (OPHTH), MSC (CEH)

   LECTURER, DEPARTMENT OF OPHTHALMOLOGY.

   UNIVERSITY OF NAIROBI, KENYA.

   SIGNED:...*Malal*................   DATE:....*29/9/08*.................

2. DR. DUNERA ILAKO,   MBCHB, MMED (OPHTH), MBA (HEALTH), FEACO.

   SENIOR LECTURER, DEPARTMENT OF OPHTHALMOLOGY.

   UNIVERSITY OF NAIROBI, KENYA.

   SIGNED:....................   DATE:....*13|10|2008*...............

3. DR. STEPHEN AKAFO

   MBCHB, FRCOphth, FWACS.

   SENIOR LECTURER, EYE UNIT, DEPT OF SURGERY,

   UNIVERSITY OF GHANA MEDICAL SCHOOL, ACCRA, GHANA.

   SIGNED:....................   DATE:....*25|11|08*...............

   Ag. Chairman
   Dept. of Ophthalmology
   UoN

DEDICATION

This study is dedicated to my wife, Cynthia Osafo- Kwaako, and my daughters Sena & Sedinam.

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LIST OF ABBREVIATIONS

APPROX	APPROXIMATELY
CAP	CAPILLARY
CI	CONFIDENCE INTERVAL.
CONJ	CONJUNCTIVA
CRAO	CENTRAL RETINAL ARTERY OCCLUSION
CRVO	CENTRAL RETINAL VEIN OCCLUSION
D	DIOPTER
DEPIG.	DEPIGMENTATION
HbSC /SC	HEMOGLOBIN SC
HbSS / SS	HEMOGLOBIN SS
IOP	INTRAOCULAR PRESSURE
KBTH	KORLE BU TEACHING HOSPITAL
OR	ODDS RATIO
PSR	PROLIFERATIVE SICKLE RETINOPATHY
RBC	RED BLOOD CELL
RD	RETINAL DETACHMENT
RPE	RETINAL PIGMENT EPITHELIUM
SCD	SICKLE CELL DISEASE
UK	UNITED KINGDOM
USA	UNITED STATES OF AMERICA
WHO	WORLD HEALTH ORGANISATION

ACKNOWLEDGEMENT

ABSTRACT

Background: The sickle cell haemoglobinopathies are a group of inherited diseases characterized by an abnormality in the B- chain of the hemoglobin molecule. The chief manifestations are chronic hemolytic anemia and vaso- occlusive crisis that produce severe pain as well as long term and widespread organ damage. The eyes offer a unique opportunity for direct observation of the vaso-occlusive process in sickle cell disease and its effects have been recorded in the conjunctiva, anterior segment, vitreous, retina and choroid. It is estimated that 1-2% of Ghana's population of approximately 25 million have sickle cell disease, with a relatively high incidence of the hemoglobin C gene, the gene that is known to be related to severe ocular manifestation in sickle cell disease. However the prevalence and pattern of ocular morbidity due to sickle cell disease in Ghana is unknown.

Objective: To determine the pattern of ocular manifestations in sickle cell disease patients at the Korle-bu Teaching Hospital in Accra, Ghana.

Study Design: Hospital-based cross-sectional study.

Study Population: Sickle cell patients reporting for routine follow up for sickle cell disease at the Sickle Cell Clinic, KBTH, Accra, Ghana.

Sampling Technique: All patients reporting for routine follow-up for sickle cell disease on the major clinic days (Monday, Thursday and Friday) at the sickle cell clinic of the Korle-bu teaching hospital during the period of the study were included in the study.

Procedure: A structured questionnaire and hospital records were utilized to collect data from the sampled subjects. Dependent variables included were age, sex, genotype and estimated number of admissions due to sickle cell crisis.
Ocular examination of patients involved the assessment of pinhole-corrected visual acuity, ocular alignment, extraocular motility and pupillary reactions. Anterior segment

examination and tonometry were carried out with a slit lamp biomicroscope and Goldmann applanation tonometer. Funduscopy was carried out with an indirect ophthalmoscope, and a detailed further examination of the fundus was carried out with a 90D lens coupled with a slit lamp biomicroscope. Fundus findings were documented with standard fundus drawings. Data collected was validated and stored in a computer for analysis. Analysis was carried out using the statistical package for social scientists (SPSS).

Results: Two hundred and one sickle cell disease patients were enrolled for the study. They comprised 67 males and 134 females; 114 HbSS subjects and 87 HbSC subjects. The ages of HbSS subjects ranged from 6 to 58 years, with a mean of 19.26 (SD11.70) years and a median age of 18 years. The ages of HbSC subjects ranged from 6-65 years, with a mean of 31.4 (SD 16.76) years and a median age of 29 years.

Visual impairment was found in 5.6% of eyes examined and was due to cataract, proliferative sickle retinopathy, optic atrophy, phthisis bulbi and CRAO. Common anterior segment signs were tortuous corkscrew conjunctival vessels, iris atrophy and cataract. These anterior segment sign were more common in the HbSC patients.

Proliferative sickle retinopathy was found in 12.9% of subjects examined. It occurred in 3.5% of HbSS patients and 25.3% of HbSC patients; 16.4% of males and 11.2% of females. The prevalence of PSR was found to generally increase with increase in systemic severity of sickle cell disease.

Conclusion: There is a high prevalence of ocular morbidity in sickle cell disease patients in the KBTH, Accra. Ocular conditions seen include unilateral decrease in visual acuity, cataract, iris atrophy, non-proliferative and proliferative sickle retinopathy.

There was an increased prevalence in ocular morbidity with increasing age, systemic severity of SCD, and the HbSC genotype of sickle cell disease patients. Sex had no significant influence on the ocular morbidity in sickle cell patients.

Eyes with iris atrophy or depigmentation were 1.8 times more likely to have PSR, however this finding may be due to chance. Anecdotally, it was observed that eyes with severer iris atrophy were likely to have severer PSR. It was concluded that the risk of

developing PSR may be related to the severity of iris atrophy rather than just the occurrence of iris atrophy or other anterior segment signs.

1.0   INTRODUCTION

The sickle cell haemoglobinopathies are a group of inherited diseases characterized by an abnormality in the B-chain of the hemoglobin molecule. The chief manifestations are chronic hemolytic anemia and vaso-occlusive crisis that produce severe pain as well as long term and widespread organ damage. [1,2,3.]

The eyes offer a unique opportunity for direct observation of the vaso-occlusive process in sickle cell disease and its effects have been recorded in the conjunctiva, anterior segment, vitreous, retina and choroid. [1,2,3,4,5,6.].

Sickle cell disease is found all over the world except in the far east and in the arctic countries. It is commonest in Africans and people of African descent. It is also common in non-black groups of Saudi Arabia and India. [1,2.].

The SS genotype forms 0.4% of the black population and leads to severe systemic disease but mild ocular disease.[1]The SC and SB-thal genotypes lead to mild systemic disease but severe ocular disease[7]. The prevalence of SC and SB-thal varies with different black populations with West Africa having the highest incidence of HbSC in Africa. [1,2.].

Historically, outside Africa, Herrick (1910) was the first to describe the symptoms and signs of this peculiar type of anemia and sickle-cell shape of the red blood cells on microscopy in a black student in Chicago[2]. However, in Africa, centuries before Dr. Herrick first met the black student with symptoms of sickle cell disease, Ghanaians new the disease syndrome and had given it various vernacular names eg. Ahututuo in Ashanti, meaning body biting. In other African countries, it was called Adep by the Banyangi of Cameroun, lakuregbee by the Yoruba of Nigeria and Nyamuoda by the Luo of East Africa[2].

Ghanaians also knew that the disease was hereditary and families with Ahututuo in Ghana have been traced to 1670 AD[2]. They described the typical presentation of cold

seasonal joint pains, pallor of the nails, tongues and palms of the hands, yellow colouring of the eyes and a poor general state of health. West Africans thought it primarily a bone and joint disease in which periodically the blood was exhausted in the patient especially during bouts of fever[2].

Ghana has a relatively high incidence of hemoglobin C when compared with that in other countries. One percent of the population of Ghana have the HbSC genotype[2]. It is generally agreed that Ghana is an ideal example of a country with a high incidence of SC genotype, the genotype that is related to severe ocular manifestations of sickle cell disease.[2.]

Hemoglobin S occurs because of a genetic defect resulting in the substitution of a single amino acid, glutamic acid by valine at position –6 of the B- peptide chain. In hemoglobin C, lysine replaces glutamic acid. Inheritance of these genes leads to SS or SC disease. [1,2,3,4]

The sickle cell gene has thrived in certain regions of the world because of balanced polymorphism. Heterozygotes have better protection from malaria than both homozygotes in malaria endemic regions. Red blood cell infection with malarial parasites leads to sickling of the red blood cell leading to phagocytosis in the spleen of both red blood cell and malarial parasites. [1,2].

The systemic manifestations are as follows:

(i).Chronic compensated hemolytic anemia with hematocrit between 18% - 30% and hemoglobin concentration between 6.5-10 g/dl. Compensation is by increased erythropoiesis leading to reticulocytosis of 10 – 25%. The anemia worsens in periods of decreased erythropoiesis eg. infection, folic acid deficiency.[1,3]

(ii).Vaso-occlusive phenomenon precipitated by dehydration, cold weather and infections. The vaso-occlusive crisis leads to bone pain crisis in the limb bones, cerebrovascular accident in the brain, acute chest syndrome in the lungs, hepatic crisis

from focal necrosis in the liver, priapism, and abdominal pain crisis due to gut infarction. The vaso-occlusive phenomenon also causes acute renal papillary infarction leading to decreased urine concentration and prolonged painless hematuria.[1,2,4]

(iii).Sickle cell disease causes chronic organ damage leading to chronic skin ulcers at the lower extremities, bony infarcts and aseptic necrosis of the femoral head common in SC disease and autosplenectomy common in SS disease. Autosplenectomy leads to an increased susceptibility to certain infections.[1,2]

(iv) Sickle cell disease patients suffer from abnormal growth and development leading to stunted growth, hypogonadism, delayed puberty and menarche, and frontal bossing[1,2].

(v) Sickle cell crisis, which is a sudden unpredictable clinical worsening of the sickle cell disease patient that would not have happened if the patient was without the sickle cell gene. The pathological classification of sickle-cell crisis includes vaso-occlusive crisis, sequestration crisis, aplastic crisis and hyperhemolytic crisis. The number and severity of sickle cell crises that a patient has suffered since birth gives some indication of the systemic severity of sickle cell disease in that particular patient[1,2].

The ocular manifestations of sickle cell disease are follows:

(i).The conjunctiva in sickle cell patients shows tortuous "corkscrew" conjuctival vessels, transient succular dilatation of vessels, and multiple, short, comma-shaped capillary segments seemingly isolated from the vascular network.[1,2,34,.]

(ii)In the anterior segment, there is an increased risk of anterior segment ischemia which in the acute stage leads to conjuctival injection, corneal edema, keratic precipitates, white deposits in the necrotic lens capsule, increased intraocular pressure and a dilated, unresponsive pupil[1]. Later, there is atrophy and depigmentation of the iris, irregularity of the pupil, cataract, rubeosis iridis and phthisis bulbi.[1] Minor traumatic hyphema leads to glaucoma leading to unexpected visual loss due to CRAO[1,2]. Sickling of haemoglobin S

cells is favoured by the relatively deoxygenated conditions in the anterior chamber. The deformed, sickled and less pliable cells are unable to negotiate the trabecular meshwork leading to increased intra-ocular pressure and predisposing to CRAO[2].

(iii) The non- proliferative changes in the posterior pole are increased tortuosity of the major retinal vessels, major branch occlusion and macular capillary loss leading to enlargement of the foveal avascular zone. However there is no relationship between this capillary loss and visual acuity. Sickle cell patients also have wedge shaped choroidal infarcts due to posterior ciliary artery occlusions, punctate red dots on or close to the disc representing transient dilatation of the superficial capillary system on the disc . They appear to be clinically unimportant. Angloid streaks may be present and increase with age.[1,3,4.]

The non proliferative changes in the peripheral retina include a pale retina with poorly defined margins due to retinal edema, and hemorrhages into the peripheral retina which are common and their sequelae depend upon their size and site. Pre-retinal hemorrhages are circumscribed, generally red lesions lying between the sensory retina and the internal limiting membrane, infront of the retinal vasculature. They are called salmon patch hemorrhages because of their colour. They resolve leaving mottled brown areas of refractile, irridescent deposits. Intraretinal hemorrhages may resolve leaving a retinoschisis cavity with irridescent deposits. These deposits are hemosiderin-laden macrophages. Hemorrhages into the deep retina or intraretinal hemorrhage tracking into the the sub-retinal space causes reaction of the RPE leading to stellate and spiculate hyperpigmentation (black sunburst sign). This is histologically due to focal hypertrophy, hyperplasia and migration of RPE cells[1,8,9].

iv) Proliferative sickle retinopathy (PSR) occurs in 5 stages which are:
I)Peripheral arteriolar occlusion;
2)Peripheral arteriovenous anastomosis which appear to be dilated pre-existent capillaries;

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3)The peripheral retina after the point of vascular occlusion is largely avascular and non-perfused leading to seafan neovascularisation;

4)Vitreous hemorrhage from the new vessels precipitated by relatively trivial ocular trauma;

5) Vitreous hemorrhage is complicated by traction retinal detachment[1,5,6].

Lesions of PSR develop from the site of abnormal arteriovenous communication at the border of the vascular and avascular retina. They occur more commonly in the temporal periphery and develop posteriorly with regression of the vascular arcades. However they may also occur at the posterior pole.[38] These abnormal vessels leak intravenously administered fluorescein. Their size and configuration vary widely from well defined vessel loops to large complex lesions that may occupy a quadrant of the retinal periphery. All lesions are supplied by a least one feeding artery and one draining vein. There are varying amounts of white fibrous tissue associated with the vascular fronds. Large lesions especially when in the mid temporal locations may exert considerable traction on the macula, thus impairing macular function, causing traction detachment, and occasionally leading to macular holes. Spontaneous regression of the PSR lesion (autoinfarction) occurs in some patients. [1,2,3,4,8].

There is no effective treatment proven to prevent neovascularisation. Therefore intervention therapy begins at the stage of seafan neovascularisation. Peripheral scatter argon-laser photocoagulation destroys the ischemic retina believed to be responsible for the proliferative retinopathy. Peripheral retinal cryotherapy is used if media opacities prevent photocoagulation. Treatment of vitreous hemorrhage and retinal detachment involves standard vitrectomy and retinal detachment surgery.[1,2,3,4,8.] However, sickle cell patients with retinal detachment do not respond favorably to conventional retinal detachment surgery.[9]

It is estimated that 1-2% of Ghana's population of approximately 25 million have sickle cell disease, with a relatively high incidence of the hemoglobin C gene, the

gene that is known to be related to severe ocular manifestation in sickle cell disease.[2] However the prevalence and pattern of ocular morbidity due to sickle cell disease in Ghana is unknown.

The influence of age, sex and genotype on ocular morbidity in Ghanaian sickle cell patients is important in the determination of the age at which ocular screening should begin and how often this screening should be carried out for each sex and genotype. Information on the influence of age, sex and genotype on the ocular manifestation of sickle cell disease in Ghana is currently unavailable.

There is no literature from Ghana on the relationship between the ocular anterior segment signs of sickle cell disease and the posterior segment signs. If a sickle cell patient is found on torchlight or slit-lamp examination to have anterior segment signs like iris atrophy or depigmentation ,what are the odds that patient will have proliferative sickle retinopathy on funduscopy? The answer to this research question will help to determine the risk of PSR in patients who are found on anterior segment examination to have signs of sickle cell disease. Consideration is given to the fact that less skill is required to perform an anterior segment exam than funduscopy. This information is helpful when designing a sickle cell ocular screening protocol for a large population.

The relationship between the systemic severity of sickle cell disease and the development of PSR is unknown. The creation of a hypothesis on the relationship between the systemic severity and ocular manifestation of sickle cell disease will also be helpful in the design of a sickle cell ocular screening protocol for a large population, with respect to identifying patients with a higher risk of developing PSR.

Patients with proliferative sickle retinopathy in Ghana usually present late to the ophthalmologist with vitreous hemorrhage or retinal detachment. This coupled with the unavailability of a specialized vitreoretinal surgery unit in Ghana makes early detection of PSR very important. The data generated from this study will describe the

magnitude and pattern of ocular features of sickle cell disease in Accra, Ghana. It will also assist in the setting of an appropriate protocol for screening, follow-up and early treatment of PSR. It will also foster a multidisciplinary approach to the management of sickle cell disease patients which will involve ophthalmologists.

A search of published literature revealed that similar studies have been carried out in Kenya[3], Nigeria[10], Senegal[11], Togo[12], Congo[13], Saudi Arabia[14], USA [15], Jamaica[16], UK[17], Brazil, and Mali, but no study was found to have been done in Ghana.

With the improvement in healthcare services for sickle cell patients in Ghana there is an anecdotal improvement in life expectancy in Ghanaian sickle cell patients. However, from the ophthalmological perspective, this increased life expectancy means that these patients will live long enough to develop the ocular complications of sickle cell disease, which if not properly managed, will impact heavily on their quality of life.

2.0   LITERATURE REVIEW.

The expansion of appropriate healthcare services worldwide has lead to the survival of most sickle cell patients into adulthood, allowing their ocular changes to become manifest and deserving of attention. Mortality attributable to sickle cell disease is decreasing and the mean age of death is increasing. Furthermore, new therapeutic strategies have been evolving for the management of sickle cell disease eg. hydroxyurea, 5-azacytidine, arginine butyrate, decitabine. This holds a promise of better healthcare for sickle cell patients leading to increased life expectancy. [3, 18]

C.T Quinn in an 18-year prospective study of 711 sickle cell subjects from birth on the issue of survival in the USA, 25 patients died in the 18 year period with a mean age of death of 5.6 years. The 711 subjects provided 5648 patient years of observation and the SCD-related survival was 93.6%. It was thus concluded that childhood mortality from SCD is decreasing and the mean age of death is increasing [18].

Visual impairment in sickle cell disease is usually unilateral. Bilateral visual loss is rare[19] Abdi Daher et al in a hospital-based study found no visual loss in 101 Kenyan patients[3.] However, Van Meurs in Curacao, in a study of 81 HbSS and 97 HbSC subjects found severe bilateral visual loss in one (1%) HbSS patient and severe unilateral visual loss in 6 HbSC patients (6%). The HbSS patient with bilateral visual loss had cortical blindness due to sickle cell-related cerebrovascular accident[20]. In Kaduna, Nigeria, Eruchalu et al reported visual loss in one out of 37 HbSS children[8] and in Lagos, Akinsola et al reported that 4 out of 99 sickle cell patients (4%) had significant visual impairment[21]. Refractive errors are more common in HbSC than HbSS subjects[22].

Conjunctival vessel signs due to sickle cell disease were observed in 87% of Kenyan patients and 81% and 77% of Nigerian patients[3,5,6]. Iris atrophy and depigmentation in sickle cell disease patients is believed to be due to the vaso-occlusive process and is closely associated with proliferative sickle retinopathy in the same eye[23]. Iris atrophy and depigmentation is more common in the male sex and the HbSC genotype [23.]

Sickle cell disease alone is sufficient as a risk factor for the development of central retinal artery occlusion. Central retinal artery occlusion in these patients leads to a pale, hazy, edematous retina; with a black spot in blacks instead of a cherry red spot[1]. Fine L.C. et al described a case of central artery occlusion in a young man with sickle cell disease and no other systemic illness nor contributing factors.[24] Multiple salmon patch hemorrhages may occur after CRAO. Reperfusion of the damaged ischemic vessels with a blow out of the walls of the vessels seems to be the most likely explanation for this phenomenon.[25]

Increased tortuosity of the major retinal vessels is a common fundus sign and occurred in 12% of Nigerian sickle cell subjects[4,21.] Salmon patch retinal hemorrhages were observed in 6.4% of Nigerian HbSS subjects. [6.] Obikili et al also found the black sunburst sign in 7.7% of Nigerian HbSS subjects[6]. The occurrence of black sunburst sign increased with increasing age. Black sunbursts are the most prevalent retinal abnormality in sickle cell patients.[24,26] Majekodunmi et al in Nigeria observed no angioid streaks in sickle cell subjects[4]. Arteriolar sheathing is another common retinal vessel abnormality in sickle cell children, occurring in 51% of HbSS children and 30% of HbSC children.[27]

Proliferative sickle retinopathy is more common in SC and SB+ thal than in SS and SBo thal[1,7] for 2 reasons: First, auto-infarction of the new vessel proliferations is more common in SS patients than in SC patients[1]. Secondly, the vaso-proliferative substance that induces the proliferative sickle retinopathy is released by the ischemic retina. The ischemic retina in SC disease is able to release this vaso-proliferative substance, but severe vaso-occlusion in SS disease leads to the dead retina not being able to release the vaso-proliferative substance[1]. Flourescein angiographic findings support the hypothesis that retinal hypoxia is an important stimulus for retinal neovascularisation[(28).]

There is no correlation between the severity of PSR and the age and sex of the patient, and the systemic complications the patient has suffered.[17] Nia et al found that there is no risk of PSR in subjects with the sickle cell trait[29], but Fani et al reported that PSR is found in subjects with the sickle cell trait but is less severe when compared with that found in sickle cell disease patients.[30] Sickle cell trait subjects may be prone to PSR after ocular trauma.[31]

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The prevalence of proliferative sickle retinopathy has been determined in hospital-based studies in Kenya, Nigeria, Togo, Saudi Arabia, Jamaica and USA. PSR prevalence in Kenya was 1% [3],Nigeria 5.6% [10], Togo 9.4% [12], Saudi Arabia 1.6%[14], USA 18%[15], Jamaica 24% [16], However, considering the PSR prevalence in HbSS patients only, 1% PSR was observed in Kenya, 1.6% in Saudi Arabia, 0% in Nigeria, 12% in Jamaica and 11% in USA. Considering HbSC subjects only, 50% PSR was observed in Curacao Island[19], 36% in Jamaica[16] and 45% in USA[15].

PSR is more common in males and its prevalence increases with increasing age in both genotypes and tended to be bilateral. There is no evidence of familial clustering. Hematological risk factors associated with PSR in HbSS disease are high Hb levels in males and low fetal Hb in both sexes, and in HbSC disease, a high mean cell volume, and low fetal Hb in females[32]. However, Talbot et al found that retinal non-perfusion correlates significantly with low total hemoglobin levels and high fetal hemoglobin, reticulocyte and irreversibly sickled cell count in HbSS disease, and with high reticulocyte count in HbSC disease.[33] Retinal non-perfusion correlated with low platelet count in HbSC disease.[34] Balo et al in Togo observed an increased prevalence of PSR with increasing age[12]. Acheson R.W. et al in their study of iris atrophy in sickle cell disease found that iris atrophy was closely associated with PSR in the same eye[23].

Proliferative sickle retinopathy was found in teenage sickle cell disease patients. It was found in 8% of males and 3% of females.[35] Although PSR occurs in teenagers, vitreous hemorrhage from PSR is rarely seen before the age of 20 years, and therefore yearly ocular examination of sickle cell patients should begin after the age of 20 years.[36]

Spontaneous regression of PSR lesions (autoinfarction) is seen in 33% of eyes with PSR and a further 39% of eyes over a follow up period of 8 years.[37,38] Autoinfarction is more common in HbSS disease than in HbSC disease.[38,39] In both genotypes, autoinfarction was not influenced by size or elevation of the PSR lesion[38] One mechanism involved in autoinfarction of neovascular tissue is progressive, centripetal retraction of the anterior vascular arcade of the peripheral retina[1]. In addition, vitreous traction of the feeder

vessels may result in sluggish blood flow and occlusion of these vessels, or may tear the seafans completely away from its feeder vessels.[39] Permanent visual loss is uncommon up to the age of 26 years in SCD patients due to autoinfarction[36.] Blindness related to PSR occurs in approximately 12% of PSR eyes.[37]

Abdi Daher Sahal et al in a study of sickle cell patients at the Kenyatta National Hospital in Nairobi, Kenya found no case of vitreous hemorrhage or retinal detachment[3]. Obikili et al in Jos, Nigeria found vitreous hemorrhage and veils in 3.8% of HbSS patients, and there were no cases of retinal detachment[6]. Balo et al found vitreous hemorrhage in 8% of Togolese HbSC patients[12]. Ndiaye et al in a study of vitreoretinal complications in HbSC subjects in Senegal found vitreous hemorrhage in 10% of the patients[11]. In Curacao, Van Meurs found PSR in 50% of HbSC patients, leading to vitreous hemorrhage in 18%, and to retinal detachment in 8%[20]. Proliferative sickle retinopathy is less common in Arab sickle cell disease patients when compared with patients of African origin because of a high fetal hemoglobin level in Arab patients.[14,40,41.]

Autoinfarction closes the feeding vessels of PSR lesions more elegantly than, and without the complications associated with photocoagulation. A greater understanding of the factors involved in the progression and regression of PSR is relevant to defining the role of photocoagulation in PSR.[37.]

Feeder vessel photocoagulation of retinal neovascularisation as a treatment modality for PSR is effective in closing the seafan and reducing the incidence of visual loss, but has a high complication rate. Examples of these complications are choroidal neovascularisation and retinal detachment. [42,43.]

Scatter argon laser photocoagulation destroys ischemic retina believed to be responsible for proliferative retinopathy. There is the localized scatter photocoagulation in which the laser burns are placed adjacent to the PSR lesions[44] and the circumferential scatter photocoagulation in which laser burns are delivered to zones of peripheral retinal capillary nonperfusion[45.]

Cryotherapy may be used if media opacities prevent photocoagulation. The single freeze thaw cycle is preferred to the triple freeze thaw cycle because the triple freeze thaw cycle caused rhegmatogenous retinal detachment, presumably related to vitreous traction on necrotic retina.[46,47]

3.0 OBJECTIVES OF THE STUDY.

3.1 General Objective

To determine the pattern of ocular manifestations in sickle cell disease patients at the Korle-bu Teaching Hospital (KBTH), Accra, Ghana.

3.2 Specific Objectives

1. To determine the prevalence of ocular morbidity amongst sickle cell disease patients in KBTH, Accra, Ghana.

2. To assess the influence of age, sex, genotype and systemic severity on the pattern of ocular findings in sickle cell disease patients at KBTH, Accra, Ghana.

3. To determine the relationship between anterior segment signs i.e. iris atrophy, depigmentation, rubeosis, and vitreoretinal changes due to sickle cell disease.

4.0   METHODOLOGY

4.1   Location of the study:

The Eye clinic /The Sickle cell clinic. Korle-bu Teaching Hospital, Accra, Ghana.

The Korle-bu Teaching Hospital is Ghana's national referral hospital with a bed capacity of approximately 2000. It is also the training centre for Ghana's College of Health Sciences comprising the University of Ghana Medical School, Post Graduate College, Dental School and the Schools of Nursing, Nutrition, Radiography, Hygiene and Laboratory technology.

The Sickle Cell Clinic in the Korle-bu Teaching Hospital (KBTH) is a unit that forms part of the Department of Medicine of the KBTH and is dedicated to the management of sickle cell disease patients in Ghana. A majority of the patients managed at the sickle cell clinic are from the Greater Accra Region of Ghana. The facility carries out prompt management of sickle cell crises, medical laboratory services and routine follow-up of sickle cell disease patients in Ghana.

4.2   Study Design:

Hospital-based cross-sectional study.

4.3   Study Population:

Sickle cell patients reporting for routine follow-up for sickle cell disease at the sickle cell clinic of the Korle-bu Teaching Hospital in Accra, Ghana.

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4.4   Sample size determination:

Minimum sample size estimation was done with a formula for cross-sectional studies. The minimum sample size estimated was 82 subjects. The values inserted into the formula were:

Estimated population size of SCD patients in Korle-bu Hospital : 50,000.
Estimated prevalence of proliferative retinopathy[21] : 5.6%
Maximum error: 5%

$$n = \frac{Z^2_{\dot{a}/2} \times P\,(1-Q)}{D^2} \qquad = \frac{1.96^2 \times 0.056 \times 0.944}{0.0025} \qquad = 81.23$$

However, 201 subjects were enrolled for this study.

4.5   Sampling Technique:

All patients reporting for routine follow-up for sickle cell disease on the major clinic days (Monday, Thursday and Friday) at the sickle cell clinic of the Korle-bu teaching hospital during the period of the study were included in the study.

4.6   Exclusion criteria:

Refusal to give consent.

Patients less than 6 years of age. This was because of the lack of special resources for ocular examination and the expected difficulty in the examination of these patients eg. visual acuity, slit lamp exam, applanation tonometry, and funduscopy.

Eyes with history of serious injuries or extensive surgery. A serious ocular injury or extensive surgery was defined as any injury to an eye or surgery, which on examination

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under slit lamp, was judged by the investigator as serious enough to modify the ocular manifestations of sickle cell disease in that injured or operated eye.

4.7   Data Collection Procedure.

A structured questionnaire (appendix 2) and hospital records were utilized to collect data from the sampled subjects. Dependent variables included were age, sex, genotype and estimated number of admissions due to sickle cell crisis.

Vision at presentation or pinhole-corrected visual acuity was assessed with a Snellen chart and illiterate E chart.

Ocular alignment, extraocular motility and pupillary light reflex was assessed for possible neurological deficits. Pupillary reactions was assessed with a pen-torch (mini maglight AAA, from mag instruments, California, USA).

Anterior segment exam and tonometry was carried out with a Carl Zeiss slit lamp biomicroscope and applanation tonometer. Tonometry was carried out only in patients who were able to cooperate with applanation tonometry. Anterior segment examination was performed to establish the presence or absence of signs due to sickle cell disease in the conjunctiva, cornea, anterior chamber, pupil, iris, lens and anterior vitreous.

Fundoscopy was carried out with a Heine indirect ophthalmoscope coupled with a Volk 20D lens. Detailed further examination of the posterior pole was performed with a volk 90D lens coupled with a Carl Zeiss slit lamp biomicroscope. Pupillary dilatation was carried out with tropicamide 0.8% and phenylephrine 5% from Aurolab, India.

Fundus findings were documented with standard retinal drawings. To reduce bias in examination, the patients' age and genotype were unknown to the examiner until completion of the data collection. Hence the age and genotype were recorded by an assistant.

4.9   Ethical considerations in data collection:

A protocol detailing the aims and methodology of this study was submitted to the ethical committee of the University of Ghana Medical School for approval before the study was carried out.

Informed written consent was obtained from patients who were recruited into the study.

Patient data was and continues to be kept confidential.

Patients with treatable ocular manifestations e.g. proliferative sickle retinopathy, cataract, etc. were offered treatment.

The results and knowledge acquired from the study will be shared with colleagues and used to the advantage of humanity and the progress of science.

4.10   Data Analysis:

Data collected was validated and stored in a computer for analysis. Analysis was carried out using the statistical package for social scientists (SPSS).

5.0   RESULTS

Two subjects in the study population were excluded for refusal of consent. Twelve subjects were excluded on account of age being less than 6 years old. Two subjects, genotype HbSBthal and HbSF were examined but excluded.

Two hundred and one subjects were enrolled for the study. 400 eyes were examined; 200 left eyes and 200 right eyes. This was because one patient had a history of trauma to the left eye with ruptured globe and having a prosthesis in left socket. Another patient had extensive surgery on the right eye which on slit lamp exam was judged to be extensive enough to modify the ocular manifestations of sickle cell disease and was therefore excluded from the study. Hence 400 eyes were examined in 201 subjects.

Two children (4 eyes) were unreliable or inconsistent in visual acuity assessment. Hence 396 eyes examined for visual acuity.

Intraocular pressure measurement was not done on 45 eyes on account of subjects being uncooperative. Another eye which had phthisis bulbi did not undergo intraocular pressure (IOP) measurement. Hence 354 eyes were examined for intraocular pressure.

Funduscopy was not successful in 3 subjects on account of subjects being uncooperative. Funduscopy was also not performed in one eye with phthisis bulbi due to the phthisis and a dense cataract. One subject gave consent for dilatation of one eye due to busy office schedule; hence a coin was tossed to dilate RE. In this patient, lens examination of LE was through an undilated pupil. Hence funduscopy was performed in 392 eyes.

Distribution by Age.

Figure 1: Distribution by age and sex. (n = 201subjects.)

P=0.007
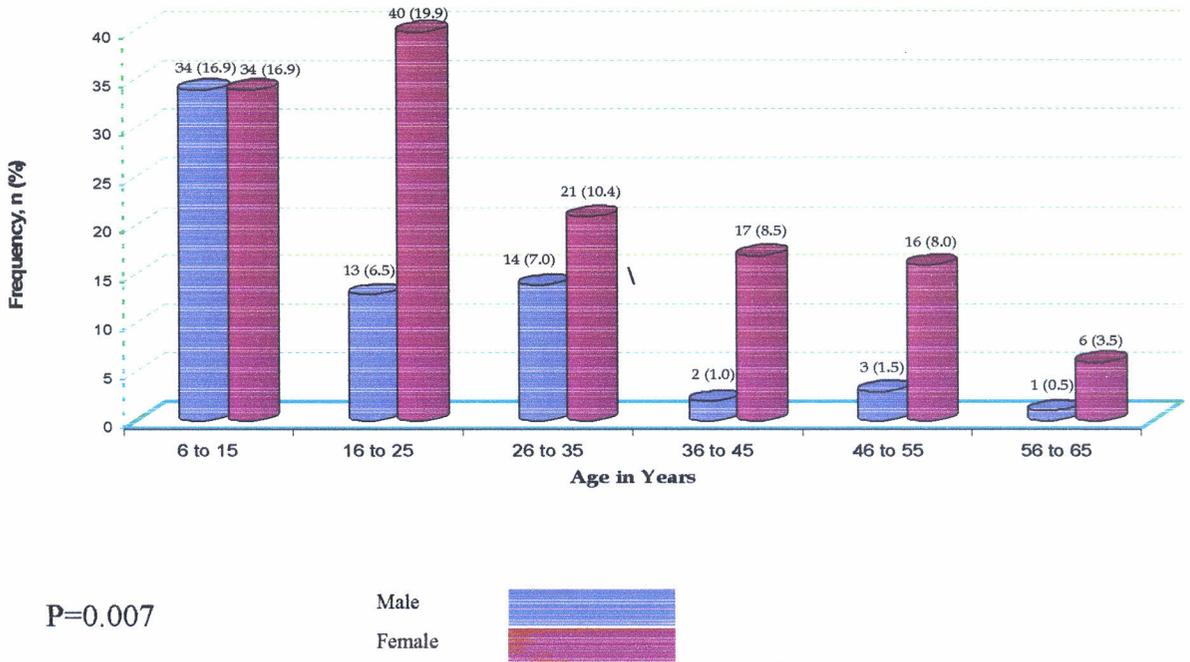
Male

Female

Two hundred and one (201) patients were enrolled with ages ranging from 6 to 65 years. The mean age was 25.52 (SD 15.3) years and the median age was 22 years. The difference between the numbers of females in the various age groups was statistically significant with p=0.007

Distribution by Sex.

Of the 201 subjects enrolled, 67 (33.3%) were male and 134 (66.7%) were female. The ages of male patients ranged from 6 to 65 years with a mean of 20.59 (SD14.7) years and a median age of 17 years. The ages of female subjects ranged from 6 to 65 years with a mean of 26.63 (SD15.29) years and a median age of 24 years.

Distribution by Genotype.

Figure 2: Distribution By Age and Genotype. (n= 201subjects) p<0.001.
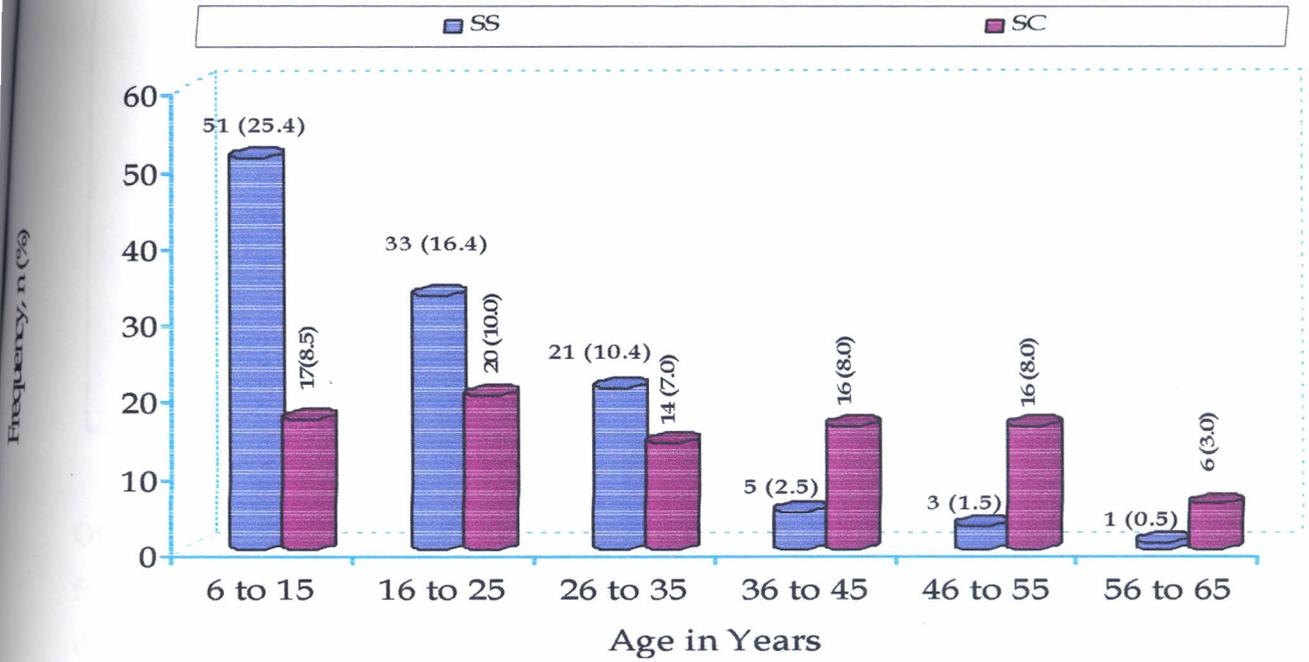
One hundred and fourteen (114) of the 201 subjects enrolled had HbSS genotype, representing 56.7% of subjects. 87 subjects (43.3%) had HbSC genotype.

The ages of HbSS subjects ranged from 6 to 58 years, with a mean of 19.26 (SD11.70) years and a median age of 18 years. The ages of HbSC subjects ranged from 6-65 years, with a mean of 31.4 (SD 16.76) years and a median age of 29 years. The differences in number of subjects for each genotype in each age group was statistically significant with p< 0.001.

Figure 3: Sex and Genotype distribution of enrolled subjects. (n= 201 subjects)

Of the 201 subjects enrolled, 48 (23.9%) were HbSS males, 66 (32.8%) were HbSS females, 22 (10.9%) were HbSC males and 65 (32.3%) were HbSC female. The difference in the number of males and females in each genotype enrolled was statistically significant with a p-value of 0.013.

Table 1: Reasons for admission of enrolled subjects and the percentage frequency for each genotype (n = 201 subjects) p= 0.063

Reasons for Admission	SS, n(%)	SC, n(%)	Total, n(%)
Bone Pain	48 (42.1)	19 (21.8)	67 (33.3)
Severe Anaemia	44 (38.6)	10 (11.5)	54 (26.9)
Malaria/Fever	28 (24.6)	15 (17.2)	43 (21.4)
Chest Pain	24 (21.1)	7 (8.0)	31 (15.4)
Abdominal Pain	24 (21.1)	10 (11.5)	34 (16.9)
Stroke	2 (1.8)	1 (1.1)	3 (1.5)
No Admissions	19 (16.7)	35 (40.2)	54 (26.9)

HbSS subjects had more previous admissions than HbSC subjects but this difference in the number of previous admissions was not statistically significant. (p=0.063)

Table 2: Admissions per year of life versus Genotype (n = 201 subjects)

Admissions per year of life	SS, n (%)	SC, n (%)
No Admission	19 (16.7)	35 (40.2)
>0 to 0.3	57 (50.0)	41 (47.1)
>0.3 to 0.6	21 (18.4)	7 (8.0)
>0.6 to 0.9	7 (6.1)	4 (4.6)
>0.9 to 1.2	3 (2.6)	-
>1.2 to 1.5	2 (1.8)	-
>1.5 to 1.8	5 (4.4)	-
Total	**114 (100.0)**	**87 (100.0)**

The total number of previous admissions a patient had had, and the number of admissions per year of life was recorded as an estimate of the systemic severity of sickle cell disease.

Admissions per year of life ranged from 0 – 1.76 admissions per year for HbSS subjects with a mean of 0.33(SD 0.39) and that HbSC ranged from 0 – 0.88 admissions per year with a mean of 0.13(SD 0.19). The mean difference of admissions per year between HbSS and HbSC was 0.20 (95%CI 0.11-0.21) and thus was statistically significant (P<0.001). Mean admissions per year of life for males was 0.35 (SD 0.44) and for females was 0.18 (SD 0.25), the difference was statistically significant with p<0.001.

Table 3: Total number of Admissions versus Genotype. (n=201 subjects)

Total number of Admissions	SS, n (%)	SC, n (%)
No Admission	19 (16.7)	35 (40.2)
1 - 2	31 (27.2)	21 (24.1)
3 – 4	21 (18.4)	9 (10.3)
5 – 6	17 (14.9)	6 (6.9)
7 - 8	5 (4.4)	5 (5.7)
≥ 9	21 (18.4)	11 (12.6)
Total	**114 (100)**	**87 (100)**

p = 0.006

The total number of previous admissions the patients had had was significantly higher in the HbSS group than in the HbSC group with p=0.006.

Table 4: Vision at presentation or with Pinhole. (n = 402 eyes)

Visual Acuity	SS, n (%)	SC, n (%)	p-value
Normal Vision	225 (99.1)	165 (95.3)	0.004
Visual Impairment	0	5 (2.9)	<0.001
Severe visual impairment	0	1 (0.6)	-
Blind eyes	2 (0.9)	2 (1.2)	-
Excluded eyes	1	1	-
Total	**228**	**174**	

All the subjects had normal vision at presentation or with pinhole in the better eye. The difference in the number of visually impaired eyes in the two genotypes was statistically significant (p<0.001)

Table 5: Reasons for vision loss in patients with visual impairment.

V/A	Reason for Vision loss	Number of eyes
Visual Impairment	Cataract	4
	Seafan neovascularisation	3
	Vitreous hemorrhage.	1
Severe visual impairment	Cataract	1
Blind	Vitreous hemorrhage	1
	Optic atrophy	1
	Phthisis bulbi	1
	CRAO	1

NB: Some eyes had more than one reason for vision loss.

Table 6: Intraocular Pressure Measurements (n=402 eyes)   p= 0.834.

IOP	SS, n (%)	SC, n (%)	Total, n (%)
< 21	189 (53.4)	159 (44.9)	348 (98.3)
≥ 21	3 (0.8)	3 (0.8)	6 (1.7)
Uncooperative subjects			45
Excluded eyes/ socket.			3

The difference in IOP measurement between the two genotypes was not statistically significant. (p=0.834). The eyes with phthisis bulbi and previous extensive surgery were excluded from IOP measurements.

Table 7: Anterior Segment signs by genotype. (n = 201 subjects)

Status	SS, n (%)	SC, (%)	p-value
Conjuctiva			
Tortuous Corkscrew conj vessels	53 (46.5)	55 (63.2)	0.018
Succular dilatations of vessels	45 (39.5)	42 (48.3)	0.212
Seemingly isolated cap segments	42 (36.8)	39 (44.8)	0.253
Injection	0	2 (1.1)	-
Jaundice	10 (8.8)	0	0.005
Iris & Lens			
Iris Depigmentation	40 (35.1)	39 (44.8)	0,161
Iris Atrophy	4 (3.5)	14 (16.1)	0.002
Rubeosis	-	-	-
Cataract	3 (2.6)	12 (13.8)	0.003

Tortuous, corkscrew conjunctival vessels, iris atrophy and cataract were more common in the HbSC genotype and the difference was statistically significant. Jaundice was more common in the HbSS genotype. (p=0.005) The average age of patients with cataract was 39.92 years (SD 15.4) with a range of 32- 65 years.

Table 8: Fundus signs versus Genotype (n = 201 subjects; 114 SS, 87 SC.)

Non-Proliferative Fundus Signs	SS, (%) (n=114)	SC, (%) n=87	p-value
Increased tortuousity of Major retinal vessels	7 (6.1)	1 (1.1)	0.072
Pale peripheral retina	24 (21.1)	27 (31.0)	0.112
Salmon patch haemorrhage	4 (3.5)	4 (4.6)	0.702
Black sun burst sign	9 (7.9)	24 (27.6)	<0.001
Angiod streaks	6 (5.3)	6 (6.9)	0.636
CRVO	0	1 (1.1)	-
CRAO	0	0	-
Proliferative Fundus Signs	SS, n (%)	SC, n (%)	P-Value
Seafan neovascularisation	4 (3.5)	22 (25.3)	<0.001
Vitreous haemorrhage	2 (1.8)	3 (3.4)	0.449
Retinal detachment	1 (0.9)	1 (1.1)	0.851

Table 9: Fundus Signs versus. Sex (n=201 subjects)

Non-Proliferative Fundus Signs	Male,(%) n=67	Female,(%) n=134	p-value
Increased tortuousity of Major retinal vessels	1 (1.5)	7 (5.2)	0.176
Pale peripheral retina	21 (31.3)	30 (22.4)	0.271
Salmon patch haemorrhage	3 (4.5)	5 (3.7)	0.872
Black sun burst sign	10 (15.0)	23 (17.2)	0.548
Angiod streaks	5 (7.5)	7 (5.2)	0.609
CRVO	0	1 (0.7)	-
CRAO	0	0	-
Proliferative Fundus Signs			
Seafan neovascularisation	11 (16.4)	15 (11.2)	0.392
Vitreous haemorrhage	1 (1.5)	4 (3.0)	0.480
Retinal detachment	0	2 (1.5)	0.299

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Table 10: Non-Proliferative Fundus Signs versus Age. (n= 201 subjects)

Non-Proliferative Fundus Signs	6 to 15	16 to 25	26 to 35	36 to 45	46 t0 55	56 to 6
Increased tortuousity of Major retinal vessels	3	2	1	0	2	0
Pale peripheral retina	16	10	6	10	8	1
Salmon patch haemorrhage	0	3	2	1	2	0
Black sun burst sign	1	9	8	6	8	1
Angiod streaks	4	1	0	4	3	0
CRVO	0	0	0	0	1	0
CRAO	0	0	0	0	0	0

Table 11: Proliferative Fundus Signs versus Age. (n = 201 subjects)

Proliferative Fundus Signs	6 to 15	16 to 25	26 to 35	36 to 45	46 t0 55	56 to 65	P-Value
Seafan neovascularisation	1 (1.6)	7 (13.2)	8 (22.9)	3 (15.8)	5 (26.3)	2 (28.6)	0.010
Vitreous haemorrhage	0	1 (1.9)	1 (2.9)	0	1 (5.3)	2 (28.6)	<0.001
Retinal detachment	0	1 (1.9)	0	1 (5.3)	0	0	0.400

Seafan neovascularisation was seen in 26 out of the 201 subjects examined. Seafans were seen in 22 out of the 87 HbSC subjects and 4 out of 114 HbSS subjects and the difference between the two genotypes was statistically significant with P< 0.001. Seafans were seen in 16.4% of males and 11.2% of females. Hence males had a higher prevalence of PSR but this difference was not statistically significant. (p=0.477). The prevalence of seafans also increased with age. (p=0.011). One out of the 68 children had seafans whilst 25 out of 133 adults had seafans. In the 56 – 65 year group, 2 out of 7 subjects had seafans. The youngest subject with seafan neovascularisation was a 14 year old female HbSS subject.

Vitreous hemorrhage was found in 5 out of the 201 subjects examined. It is observed in 2 out of 223 HbSS subjects and 3 out of 169 HbSC subjects. This was more common in HbSC subjects but the difference was not statistically significant with p=0.499. Vitreous hemorrhages were also more common in females but the difference between the two sexes was not statistically significant with p=0.480. It was observed in 1 out of 67 males

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and in 4 out of 134 females. Vitreous hemorrhage was seen to be significantly more prevalent with increasing age with p<0.001.

Retinal detachment was found in 2 out of the 201 subjects examined. All the eyes involved were female, but the difference in the prevalence of retinal detachment between males and females was not statistically significant. (p=0.99). There was no significant association or correlation between retinal detachment and age or genotype.

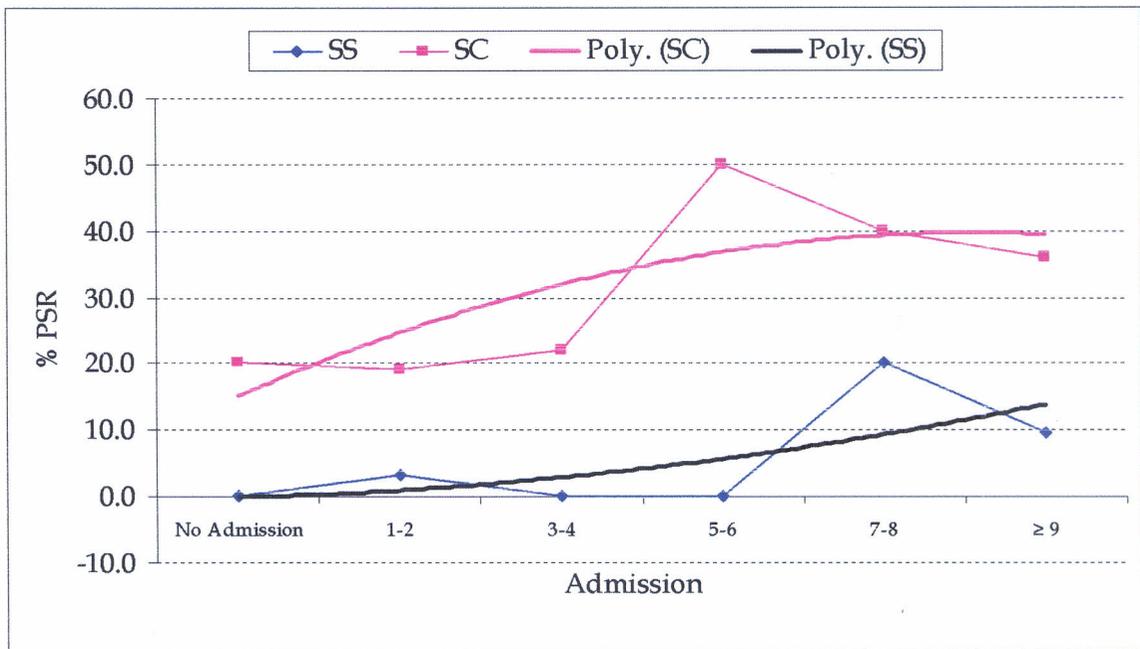**Figure 4: Total number of admissions versus Genotype and PSR prevalence.**

Figure 4 shows that the prevalence of PSR increases with increasing total number of admissions a patient has had as a result of sickle cell crisis for both genotypes.

Figure 5: Admission per year of life versus Genotype and PSR prevalence.
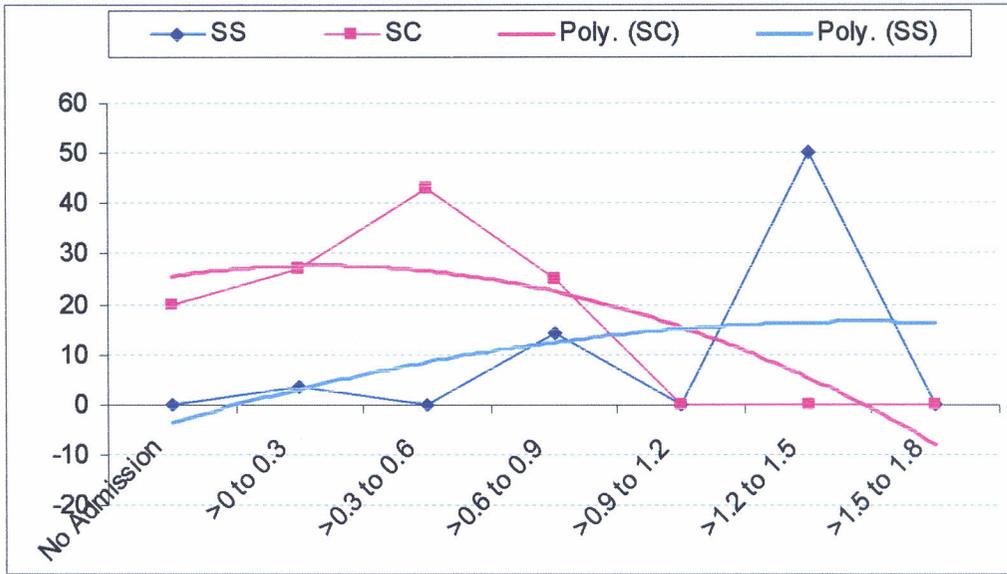
Figure 5 show that the prevalence of PSR first increases, and then decreases with increasing admissions per year of life in HbSC subjects, but increases with increasing admissions per year of life in HbSS subjects.

Table 12: Association between Iris Atrophy/Depigmentation and PSR.

		PSR			
		Yes, n (%)	No, n (%)	OR (95% CI)	P-value
Iris Atrophy/	Yes	20 (5.3)	154 (38.9)	1.8 (0.8-3.8)	0.150
Depig.	No	15 (3.9)	203 (51.8)		

Table 12 shows that eyes with iris atrophy or depigmentation are 1.8 times more at risk of PSR than eyes without iris atrophy or depigmentation with a 95% confidence interval of 0.8 – 3.8 times, but the association was not statistically significant (p= 0.150). This finding is by chance because the OR includes 1.

Table 13: Category- based Prevalence of PSR in different categories of Sickle Cell Patients.

Subgroup Selected for Analysis.	Percentage PSR %
Total subjects (n=201)	12.9
SS subjects only (n = 114)	3.5
SC subjects only (n=87)	25.3
Children only (n=68)	1.5
Adults only (n=133)	18.8
SS adults only (n = 63)	4.8
SC adults only (n = 70)	31.4
SS adults only, with admission (n = 54)	5.6
SS adults only, with no admission (n = 9)	0
SS adults only, with Admission per year > 0.3 (n = 16)	12.5
SS adults only, with admission per year >0.6 (n = 8)	25.0
SS adults only, with admission per year <= 0.6 (n = 55)	3.6

6.0   DISCUSSION

1. Age, Sex and Genotype of Enrolled Subjects.

There was a rapid decline in the number of subjects enrolled with increasing age. Sixty eight (33.8%) of the subjects enrolled were children between the ages of 6-15 years, and the number decreased continuously to 7 (3.5%) between the age of 56-65 years. (Figure 1).This reflects the lower life expectancy of sickle cell patients when compared with the general population. Life expectancy at birth in Ghana in the year 2005 was 59.49 years for the general population; 58.65 years for males and 60.35 years for females[48]. CT Quinn, in an 18 year prospective study of 711 sickle cell subjects from birth on the issue of survival, 25 patients died in the 18 year period with a mean age of death of 5.6 years[18]. It was also observed in this study that there was a steeper decline in the number of HbSS subjects with increasing age when compared with HbSC subjects. Fifty-one HbSS children were enrolled and this number rapidly decreased to 1 in the 56-65 years group. Seventeen children with HbSC were enrolled and this number gradually decreased to 6 in the 56-65 year group. (Figure 2). This is due to the fact that the HbSS sickle cell disease is severer and leads to a greater reduction in the life expectancy of HbSS patients when compared with that of HbSC patients [1,7].

In childhood, males and females were found to have equal attendance at routine medical check up, but in adulthood, the females had a higher attendance at routine medical check-up (p=0.007). (Figure 1). This may be due to the anecdotal issue of adult females being more compliant to chronic health care issues than adult males. Both male and female children were dependent on parental compliance and were usually brought to the routine medical check up by an adult sister or mother whose compliance was evident equally in male and female children. This study (Figure 1) also depicts the possibility of females having a higher life expectancy when compared with males. Females in the Ghanaian general population have a higher life expectancy [48]. The higher life expectancy in females may be due to a genetic or physiological advantage of the female sex, or due to just a better compliance to health care issues by the female sex.

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2) Systemic Severity of Sickle Cell Disease in Enrolled Subjects

The total number of admissions due to sickle cell crisis and the number of admissions due to sickle cell crisis per year of life gives an indication about the systemic severity of sickle cell disease. (Tables 2&3). No literature was found on the use of sickle cell crisis admissions as an estimate of systemic severity of sickle cell disease.

Nineteen of the 114 HbSS patients (16.7%) and 35 of the 87 HbSC (40.2%) were found to have had no previous admissions. The highest number of admissions for HbSS patients was approx 50 and that for the HbSC patients was approx 40. Comparing the trend of patient numbers as the number of admissions increased for HbSS and HbSC led to the expected inference that HbSS is systematically more severe than HbSC[7]. The data also showed a mean difference of 0.20 admissions per year of life between HbSS and HbSC genotype with a 95% confidence interval of 0.11 – 0.29 with P< 0.001. It was thus inferred that, considering admissions per year of life, HbSS is systematically more severe than HbSC and the probability that this inference is by chance is negligible.

The mean admissions per year of life for male subjects was 0.35 (SD 0.44) and that the females was 0.18 (SD 0.25) and the difference was statistically significant with p<0.001. This implies that males may have a more severe sickle cell disease. However, the fact that very few male adults with HbSC came for routine check-up may have biased the results. Therefore, male patients who had less severe disease failed to report for routine medical check up, leaving the male subjects with severer disease to enroll.

Most of the patients were admitted for bone pain crisis, severe anemia requiring blood transfusion or malaria/fever. Some patients were also admitted for chest or abdominal pain crisis and 3 patients were admitted with a cerebrovascular accident (Table 1). No patient had admission for the ocular manifestations of sickle cell disease, although 5.6% of eyes examined in this study were found to have had painful or blinding ocular manifestations of sickle cell disease. Patients, healthcare workers and policy makers

focus on the life-threatening manifestations of sickle cell disease leading to the partial neglect of sight-threatening ocular manifestations.

3) Visual acuity.

Most of the eyes (99.1% of HbSS and 95.3% of HbSC eyes) had normal vision at presentation or with pinhole correction according to the WHO classification. (Table 4). Only 2.5% of the patient eyes had visual impairment, half of which had severe visual impairment or blindness. However, all the patients had normal corrected vision in the better eye. This is in agreement with the Caracao study, in which researchers found that bilateral blindness due to sickle cell disease was rare; the only bilateral blindness found in that study was as a result of cortical blindness from a cerebrovascular accident due to sickle cell disease.[19]Hence, visual loss from sickle cell disease is not of serious public health significance. However, this unilateral visual loss is significant for the individual patient who is also saddled with the systemic complications of SCD and the fear of losing vision in the better eye. This is coupled with the loss of stereopsis and decreased visual field resulting in an increased risk of injury to the better eye.

Visual loss in HbSC patients was found to be more frequent than in HbSS patients and was due to proliferative and non-proliferative changes in the retina. This visual loss was less severe compared with that of the HbSS patients whose visual loss was due to anterior segment ischemia and CRAO/CRVO. However, visual loss in HbSS subjects was found to be less frequent. (Tables 4&5)

4) Anterior segment findings.

Conjunctival vessels signs were found in 40-53% of enrolled subjects with approximately equal prevalence amongst HbSS and HbSC patients. (Table 7) This was a much lower prevalence compared with the 87% conjunctiva vessels signs found in Kenyan patients

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and the 81% and 77% found in Nigerian subjects.[3,5,6] Conjuctival signs found in the subjects were of very variable severity. Conjuctival vessel signs found in our study were tortuous corkscrew conjuctival vessels, succular dilatation of vessels, seemingly isolated capillary segments.

Ten of the 201 subjects enrolled had some degree of bilateral jaundice. All the 10 patients with jaundice had the HbSS genotype due to the increased severity of the hemolytic crisis in HbSS subjects. However, only 2 patients complained of jaundice as an ocular symptom in this study. Icterus was found in 50.5% of the patients in the Lagos study [21]. This was a much higher figure when compared with the prevalence of jaundice found in this study.

Cataract and iris atrophy/depigmentation was 3 times more prevalent in subjects with HbSC than HbSS. (Table 7). It was observed that cataracts occurred in a younger age group in sickle cell patients than the general population. The average age of cataract patients in this study was 39.92 years with a range of 32-65 years. No rubeosis was found on slit lamp examination.

Only 1.7% of eyes examined had IOP measurements had IOP >21 mmHg. (Table 6). These subjects were not known glaucoma patients and had no optic disc signs of glaucoma. However, Abdi Daher et al found normal IOPs in all the Kenyan patients examined.[3] Two subjects who were known cases of glaucoma had normal IOP on treatment with ocular hypotensives.

5) Fundus signs.

Increased tortuosity of the major retinal vessels was significantly more prevalent in HbSS subjects than HbSC subjects, and in females more than males. There was no correlation with age (Tables 8,9,10,11). Increased tortuosity of major retinal vessels was the most common fundus sign in a Nigerian Cohort and it was found in 12% of another

Nigerian cohort [4,8]. A 12 year old female subject was seen to have markedly increased tortuosity of major retinal vessels appearing as zig-zag lines in the fundus.

Peripheral retinal pallor was found in 21.1% of HbSS subjects and 31.0% of HbSC subjects enrolled. There was no significant association sex, genotype or the development of PSR . Fifty percent of the children examined had pale peripheral retinas but only 1.6% of the children had PSR.

Salmon Patch hemorrhages or the retina were seen in 2.8% of subjects with no significant association with age, sex or genotype. This proportion was less than half of the 6.4% found in HbSS patients in Jos, Nigeria by Obikili et al[6].

In this study, the black sunburst sign was seen in 12% subjects enrolled. It was seen in 21.2% of the HbSC patients and 5.0% of HbSS patients with an approximate ratio of 4:1 (p<0.001) indicating that the black sunburst sign was significantly more common in HbSC subjects. The black sunburst sign was seen in approx 12% of both females and males, however, the prevalence of black sun bursts seen to increase with increasing age. (Tables 8,9,10). Obikili et al also found the black sunburst sign in the fundus of 7.7% of HbSS subjects. This prevalence increased with increasing age[6].

Angioid streaks were found in 5.3% of HbSS subjects and 6.9% of HbSC subjects examined. The higher prevalence of angioid streaks in HbSC (P=0.503) and male subjects(P=0.470), was not statistically significant. However Majekodunmi et al in Nigeria observed no angioid streaks in HbSS subjects[4]. Angioid streaks represent crack-like dehiscences in the elastic layer of Bruch's membrane due to an abnormal fragility of the basal lamina caused by a degenerative process combined with calcium deposition. This results in secondary changes in the RPE and choriocapillaries. Angioid streaks are seen on funduscopy but initially may be very subtle and easily overlooked. It also observed on fundus flourescein angiography as RPE window defects over the streaks. The diagnosis of early angioid streaks on screening funduscopy is difficult and may be

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under diagnosed or over estimated. This may explain the wide variation in the prevalence of angioid streaks, between that seen by Majekodunmi et al [4] and this study.

A case old central retinal vein occlusion was seen in a 48 year old female HbSC patient with marked epiretinal gliosis and pigmentary changes in the fundus. No cases of central retinal artery occlusion were observed in this study. (Tables 8,9,10)

A forty year old female, HbSS patient was found to have an early chloroquin maculopathy with some pigmentary changes at the macular. The patient had been using chroloquin tablets for malaria prophylaxis for more than 10 years.

Seafan neovascularisaton was seen in 12.9% of subjects examined(Tables 8,9,10,11). The prevalence of proliferative sickle retinopathy varies in different countries and is based on the life expectancy of sickle cell patients in the country and presence or absence of the HbSC genotype. The prevalence of PSR in Kenya is 1%, Nigeria 5.6%, Togo 9.4%, Saudi Arabia 1.6%, Jamaica 24%, and USA 18%[3,10,12,14,15,16]. Similar PSR prevalence results were obtained in Ghana, Nigeria and Togo because these countries have HbSS and HbSC populations with similar life expectancy. Kenya and Saudi Arabia have only HbSS populations leading to a lower PSR prevalence compared with Ghana. Jamaica and USA have a higher PSR prevalence because of a higher life expectancy in sickle cell disease patients resulting in an older sickle cell population. Seafans were seen in 25.3% of HbSC subjects and 3.5% of HbSS subjects and the difference was statistically significant (P<0.001). Sea fans were observed in 16.4% of male subjects i.e. 16.4% and 11.2% of female subjects but the difference was not statistically significant (p=0.477), even though Fox et al found a statistically significant increased prevalence of PSR in males[32]. The prevalence of seafan neovascularisation in this study was seen to increase with age (P=0.011). This is deduced from the fact that only 1.5% children had seafans compared to 18.8% of adults. In the extreme age group of 56-65 years 28.6% had seafans. The youngest subject with seafan neovascularisation was a 14 year old female HbSS subject. Balo et al in Togo found 20.6% PSR in the 15-24 year group. 23.8% in the 25-34 year

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group and 15% in the 35-44 year group with no significant increase in the prevalence of PSR with age[12].

Vitreous hemorrhage was seen in 2.5% of subjects examined, 1.8% of HbSS subjects and 3.4% of HbSC subjects. The difference was not statistically significant (p=0.499). The higher prevalence of vitreous hemorrhage in HbSC subjects is as a result of higher prevalence of seafan neovascularisation which bleed either spontaneously or after trivial trauma. The 1.8% prevalence of vitreous hemorrhage in HbSS subjects is more than the 0% found in Kenyan HbSS patients but less than the 3.8% found in Nigerian HbSS subjects[3,6]. The 3.4% prevalence of vitreous hemorrhage found in HbSC patients is much lower when compared with the 10%, 8% and 18% found by workers in Senegal, Togo and Curacao respectively [11,12,19]. Vitreous hemorrhage was also seen to be more common in females but the difference was not statistically significant (P=0.480). It was seen in 1.5% of males and 3.0% of females. Vitreous hemorrhage was seen to be significantly more prevalent with increasing age.(p<0.001). (Tables 8,9,11). There is a statistically significant increase in prevalence of vitreous hemorrhage with age. Vitreous hemorrhage is more common in females because females have a higher life expectancy.

Retinal detachment was found in 1% of subjects examined. It was seen in 0.9% of HbSS subjects and 1.1% of HbSC subjects. This prevalence in HbSS subjects in this study is more than the 0% retinal detachment found in Kenyan and Nigerian patients[3,6]. However, the prevalence of retinal detachment in HbSC subjects in this study is much lower compared with the 8% prevalence found by Van Meurs in Curacao[20]. The higher prevalence of retinal detachment in Curacao may be related to the higher PSR prevalence of 50%. All the involved eyes were that of female subjects but the sex difference was by chance (p=0.99). There was no significant associaton between retinal detachment and age or genotype in this study. One patient had traction retinal detachment with vitreoretinal bands and epiretinal membranes. The other patient had a rhegmatogenous retinal detachment occurring as a result of a retinal hole in a retinoschisis cavity (Tables 8,9,11).

6) Correlation between anterior segment signs and PSR

In our analysis, eyes with iris atrophy or depigmentation are 1.8 times at risk of developing PSR than eyes without these iris signs (95% CI 0.8-3.8).However the 95% confidence interval indicates that these iris signs may be protective against PSR. It must however be emphasized that the eye with the severest iris atrophy in this study also had the most florid seafan neovascularisation in the posterior segment. (Table 12). Acheson R. W. et al in the study of iris atrophy in sickle cell disease found that iris atrophy was closely associated with proliferative sickle retinopathy in the same eye[23]. However, the results of this study indicates that the increased risk of having PSR is related to the severity of iris atrophy rather than the just the presence of iris atrophy.

7) Correlation between systemic severity of sickle cell disease and PSR

Patients with HbSS have a worse systemic severity than HbSC patients, but HbSC subjects have a higher risk of PSR[7]. Health workers may be tempted to reason that a decreased systemic severity of sickle cell disease leads to an increased risk of PSR.

In this study, it was found that for the patients with HbSC, 20% of patients with no previous admissions had PSR and 26.8% of patients with admissions but admissions per year of life $\leq$0.3 had PSR. This percentage rose sharply by 42.9% for those with admissions per year of life >0.3 to 0.6, and then fell to 25% for those with admissions per year of life >0.6 to 0.9, creating a dome-shaped distribution. (Fig 5). The inference was that for patients with HbSC, a moderate systemic severity increases the risk of PSR when compared with the low or high extremes of systemic severity.

However, for patients with HbSS, there was a positive correlation between PSR and the systemic severity of sickle cell disease. In patients with no admission, no PSR was found, and 5.3% of patients with admissions per year of life >0-0.03 had PSR. This percentage

rose sharply to 14.3% in patients with admissions per year of life >0.6-0.9, then to 50% in patients with admission per year of life >1.2- 1.5. (Fig 5). This indicates that in HbSS patients, apart from the low general prevalence of PSR, patients with no previous admissions due to sickle cell crisis are less likely to have PSR and the risk of having PSR increases with increasing number of admissions per year of life.

The results of this study also showed that the risk of development of PSR increased with the total number of admissions that a patient has had, for both HbSS and HbSC subjects. (Fig 4). The total number of admissions a patient has had is related to the age of the patient and hence older patients are likely to have more admissions, but their increased prevalence of PSR may be related to their age rather than the total number of admissions.

However, the power of this correlation between systemic severity and PSR is low because of the relatively few number of eyes with PSR, especially in the patients with HbSS. Kent et al in the United Kingdom studied the relationship between the systemic complications of SCD and PSR and found no correlation between the systemic complications and PSR[37].

8) Analysis of patients with increased risk for PSR

The results in table 13 show that the risk of developing PSR in SCD patients is not evenly spread throughout the sickle cell population. The prevalence of PSR found in Ghanaian sickle cell patients is 12.9%, however, the prevalence of PSR varies with different subgroups of the sickle cell population. HbSC adults have the highest prevalence of PSR , with a prevalence of 31.4%. HbSS patients have a PSR prevalence of 3.5%, but HbSS adults with admission per year of life > 0.6 have a PSR prevalence of 25.0%.

From our analysis, a PSR screening program with limited resources should consider HbSC adults who have a PSR prevalence of 31.4% and HbSS adults with admissions per year >0.6 who have a PSR prevalence of 25.0%. This protocol will leave out children, who have a PSR prevalence of 1.5% and HbSS adults with admission per year of life

≤0.6 who have a PSR prevalence of 3.6%. According to our study, no HbSS patient without admission due to sickle cell crisis had PSR and thus, this group can safely be left out in PSR screening. However, all sickle cell patients with frank iris atrophy on anterior segment exam should have a screening funduscopy to rule out PSR.

This study examined 201 subjects with sickle cell disease with a PSR prevalence of 12.9%. Seventy HbSC adults were examined out of which 22 subjects had PSR. Also, 8 HbSS adults with admission per year >0.6 were examined out of which 2 had PSR. This means that, if the above high risk protocol should be followed, only 78 of the 201 subjects i.e. about 40%, would have to be examined and 24 out of the 26 PSR subjects would be diagnosed. Only 2 out of the 26 subjects with PSR (2 HbSS subjects) would be sacrificed, and the chances that PSR in these 2 subjects will lead to blindness is still very low due to the already accepted increased incidence of autoinfarction in HbSS patients.

9) Comparison of the occurrence of PSR in different countries

Considering the occurrence of PSR in various countries with sickle cell disease, the prevalence of PSR amongst sickle cell disease patients was similar in Ghana (12.9%), Togo(9.4%)[11] and Nigeria (5.6)[9]. However, Saudi Arabia and Kenya had a low percentage of 1.6%[18] and 1%[3] respectively because all the patients had the HbSS genotype. Jamaica[16] and USA [15] recorded a high prevalence of 24% and 18% respectively.

The higher prevalence of PSR in USA patients may be due to the increased survival resulting from improved medical services. The consequence is a higher number of patients surviving into adulthood to develop PSR.

However, considering PSR prevalence in HbSS patients only, Kenya 1%, Nigeria 0%, Saudi Arabia (1.6%) and Ghana 2.2%, there was less difference between the various countries. The 12% in Jamaica and 11% in USA was probably due to increased longevity

from improved health care services. This shows that the prevalence of PSR in a population is influenced by the presence or absence of the HbSC genotype.

The prevalence of PSR in HbSC patients in all the studies found in literature search was very high. However, this prevalence was up to 2 times higher in Caracao Island 50%, Jamaica 36% and USA, 45%, than that found in Ghana (25.3%). This high prevalence of PSR in Jamaica and USA may be due to the availability of improved healthcare services resulting in a higher life expectancy. This allows these patients to survive into adulthood and develop PSR.

7.0   CONCLUSION

There is a high prevalence of ocular morbidity in sickle cell disease patients in the KBTH, Accra. Ocular conditions seen include unilateral decrease in visual acuity, cataract, iris atrophy, non-proliferative and proliferative sickle retinopathy.

The study also observed that there was an increased prevalence in ocular morbidity with increasing age and the HbSC genotype of sickle cell disease patients. Sex had no significant influence on the ocular morbidity in sickle cell patients.

The prevalence of PSR in HbSS subjects increased with increased systemic severity. However, with HbSC subjects, the prevalence of PSR increased with moderate increase in systemic severity and is decreased at the low and high extremes of systemic severity. It was also observed that HbSC adults, and HbSS adults with admissions per year more than 0.6 were particularly at increased risk for the development of PSR. Hence these two groups should be given priority in ocular screening programmes.

This study found that eyes with iris atrophy or depigmentation are 1.8 times more likely to have PSR, but this increased risk was just by chance. Anecdotally, it was observed that eyes with severer iris atrophy were likely to have severer PSR. It was concluded that the risk of developing PSR may be related to the severity of iris atrophy rather than just the occurrence of iris atrophy or other anterior segment signs.

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8.0   RECOMMENDATIONS

A further study with increased number of subjects should be carried out to increase the power of these results and conclusions. Otherwise, a multicentre study can be carried out in different geographical locations and a metanalysis performed. It is also important that a prospective study is carried out to obtain a more accurate record of systemic severity in terms of the actual number of admissions and the number of days for each admission.

It is suggested that a screening protocol for PSR in Accra be designed with the focus on HbSC adults and HbSS adults with previous admissions due to sickle cell crisis. This will lead to the early detection and management of PSR in Ghana.

There is the need for genetic research into other genes, apart from the sickle cell gene, that may be responsible for the development of PSR and autoinfarction of PSR lesions.

Sickle cell patients, health workers and policy makers should give equal priority to the sight-threatening and life-threatening complications of sickle cell disease, because blindness will have a serious impact on the quality of life of these patients.

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APPENDIXES

APPENDIX 1: CONSENT FORM

I _____ of _____ hereby give

Consent to be included in this study.

I further state that the eye examination procedures have been explained to me and I fully

understand what is to be done.

Date _____

Signed _____

I confirm that I have explained the nature and effect of the procedures, which involve

retinoscopy, slit lamp examination, measurement of intraocular pressure by Goldmann

Applanation Tonometry and dilated funduscopy using indirect ophthalmoscope, 90D lens

and a Goldmann 3-mirror contact lens.

I also agree that all patient information will be kept confidential.

Date _____

Signed _____

APPENDIX II: QUESTIONNAIRE.

Date

Patient Number

Number of Admissions

Reasons for Admission

           Severe Anaemia

           Bone Pain

           Abdominal Pain

           Chest Pain

           Malaria/Fever

           Stroke

Ocular History

V/A   RE   LE   Extraocular Motility.

S.L.E -   Pupil

        Conjunctiva

           -   Tortuous corkscrew conj. Vessels

           -   Transient succular dilatation of vessels

           -   Seemingly isolated capillary segments

           -   Injection

           -   Jaundice

        Iris

           -   Depigmentation

           -   Atrophy

           -   Rubeosis

Lens

- Cataract

Other signs depending on history

IOP   RE

                 LE

Fundus

- Increased tortuosity of major retinal vessels
- Pale peripheral retina
- Salmon patch hemorrhage
- Black sunburst sign
- Angioid streaks
- Sea fan neovascularisation
- Vitreous hemorrhage
- Retinal detachment

Other Fundus signs

Fundus drawing

Date ....

Patient No.	Hospital No.	Age	Sex	Genotype
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