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THE PREVALENCE OF RETINOPATHY AMONG PATIENTS WITH SICKLE CELL DISEASE

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Abstarct

Sickle cell anemia is an inherited disorder characterized primarily by chronic hemolytic anemia and vaso-occlusive crises. It affects millions of people throughout the world. There is no tissue or organ spared from injury by sickling disorder including the retina.

This studt aimed to determine the prevalence of retinopathy among patients with sickle cell disease.

The study was done on 120 subjects, 60 patients and 60 healthy control. Beside electrophoretic testing, all subjects underwent careful ophthalmoscopic examination (direct and indirect) by the same examiner.

The American academy of Ophthalmology criteria for diagnosing and staging of sickle retinopathy was followed in this study.

Retinopathy was more common patients with sickle cell disease (16%), than in control group (3%). Those with SF hemoglobin were seem to be affected more than the other studied groups (AS, SS). Male patients and those who were above 40 years showed more prevalence of retinopathy.

Introduction

Sickle cell anemia is an inherited disorder characterized primarily by chronic anemia and periodic episodes of pain.

It is caused by an error in the hemoglobin(Hb) gene resulting from point mutation that results in glutamic acid to valine subsitution in the sixth amino acid of the beta globin gene[1,2].

Hemoglobinopathies occur in a heterozygous or homozygous form. The most common form of sickle hemoglobinopathy is the heterozygous state, known as sickle cell trait (Hb AS), in which the RBC contains normal HbA together with abnormal Hb S.

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Other types of hemoglobinopathies are Hb SS, Hb SC, and Hb S—thalassemia (β^0 or β^+). Hb SS is associated with the most severe systemic manifestations and often early morbidity.

Although the systemic manifestations of sickle cell trait are usually mild or absent, patients with sickle cell trait may develop ocular complications[3].

The oxygenated HbS and HbA types are equally soluble, however, the solubility of deoxygenated HbS is severely reduced.

The insolubility of deoxy-HbS is related to the presence of point mutation in hemoglobin gene and to the resultant increased surface hydrophobicity of HbS molecule[1]. The solubility of deoxy-HbS is 17 grams per deciliter, far less than the usual 34 gram per deciliter

concentration of hemoglobin within sickle erythrocyte.

Upon deoxygenation, super saturation, aggregation and polymerization of deoxy-HbS occur rapidly, with the progression from nuclear aggregation to polymer formation having delay time inversely related to the 30th power of deoxy-HbS connection. Resultant polymer fibers provide additional nuclei for further polymer formation[2].

In sickle cell anemia ,after the hemoglobin molecules give up their oxygen, some of them may cluster together and form long rod like structures. These structures cause the red blood cell to become stiff and to assume a sickle shape.

Unlike normal red cell, which are usually smooth and biconcave shaped, the sickle cell cannot squeeze through small blood vessels, instead they stack up and cause blockage that deprive the organs and tissues from oxygen[4].

The organs at greatest risk are those with venous sinuses where blood flow slow and oxygen tension and PH are low like spleen and bone marrow or those with limited terminal arterial blood supply like the eye, the head of femur, humerus and the lungs[5,6].

Previous study conducted in Basrah province revealed that the prevalence of sickle cell disease was 2.5% for sickle cell anemia and 16% was sickle cell trait[7].

Since the viscosity of blood is proportional to the hematocrit, the reduced viscosity associated with homozygous sickle cell anemia may protect against vascular occlusion.

In contrast, patients with Hb SC and Hb S-β-thalassemia hemoglobinopathies have higher hematocrits, causing higher whole blood viscosity and a relatively increased frequency of vascular occlusions in the retina[8].

Ophthalmic complications of sickle cell disease include tortuousity of conjunctival vessels, anterior chamber ischaemia, retinal artery occlusion, angioid streaks, proliferative retinopathy, and retinal detachment and haemorrhage[1].

Vaso-occlusion is the initial event in sickle cell retinopathy. Vascular beds with low flow and high oxygen extraction are more prone to sickling and secondary vascular occlusion. The peripheral retina and macula appear to be the most susceptible to vascular occlusion[9].

The vascular occlusions of sickle cell retinopathy occur in the arterioles rather than in the capillaries, perhaps because the sphincters of the precapillary arterioles are narrower than the true capillaries[10,11].

Patients and Methods

A total of 60 patients with sickle cell disease who were admitted or attended Basrah teaching and General hospitals (32 males and 28 females) were studied Their ages ranged between 15 and 60 years with a mean age of 37.5 years. Compared to 60 apparently healthy, age and sex matched control subjects (30 male and 30 female), all were resident doctors, medical students, and paramedical staff, who had no or any family history of sickle cell disease or other significant medical history.

The study was conducted during the period from December 2003–July 2004. Patients with diabetes mellitus, hypertension, and other cardiovascular disease were excluded from the study.

A full clinical examination was performed for each patient and control subject.

A detailed eye and both retina examination was carried out by one ophthalmologist (the supervisor), using direct, indirect ophthalmoscopy and Goldmann three mirror lens with a slit-lamp 20 minutes after local application

of a mydriatic agent (Tropicamide 1%) 2 drops in each eye.

Hemoglobin electrophoresis were done for each patient and control subject using cellulose acetate electrophoresis; unfortunately hemoglobin variant was not available at the time of conducting the study. Accordingly 3 groups (each of 20) with SS, AS, and SF hemoglobin were studied respectively.

The following criteria were used in diagnosing and staging sickle retinopathy:

proliferative sickle retinopathy

*Stage*1 peripheral arteriolar occlusion.

*Stage*2 peripheral arteriovenous anastomosis. The retina after the point of vascular occlusion is largely avascular and non-perfused.

*Stage*3 consists of sprouting of new vessels from the anastomosis.

(a)Initially, the new vessels lie flat on the retina and have a fan-shaped configuration (sea-fan neovascularization).

(b)Sea-fan spontaneously involutes as a result of autoinfarction.

(c)The remaining tufts become adherent to the cortical vitreous gel and are pulled into the vitreous cavity and may bleed .

*Stage*4 vitreous hemorrhage which may be resulted from trivial trauma.

*Stage*5 fibrovascular proliferation, vitreoretinal traction and retinal detachment.

Non-proliferative sickle retinopathy

Asymptomatic lesions:

(a)Venous tortuosity due to peripheral arteriovenous shunt.

(b)Silver wiring of arterioles in peripheral retina, which represent previously occluded arterioles .

(c)Salmon patches are pink preretinal or superficial intraretinal haemorrhage at the equator which are adjacent to the arterioles.

(d)Blank sunbursts are patches of retinal pigment epithelial hyperplasia.

(e)Macular depression sign is an oval depression of the bright central macular reflex due to atrophy of the sensory retina.

(f)Areas of peripheral whitening.

(g)Peripheral retinal tear(are asymptomatic unless they cause vitreous hemorrhages or retinal detachment).

Symptomatic lesions :

(a) Macular arteriolar occlusion.
(b) Central retinal artery occlusion.
(c) Retinal vein occlusion.
(d) Choroidal vascular occlusion.
(e) Angioid streaks[12].

Statistical analysis was done by Z-test, P value <0.05 is considered to be statistically significant.

Results

One hundred and twenty subjects were included in this study, 60 patients with sickle cell disease, and 60 apparently healthy control subjects.

Table I showed the distribution of all patients and control subjects according to their age group and sex.

Twenty three (37%) of patients, and 25 (41%) of control subject were in the age group of 26-35 year.

Our observations showed that neither the patients group nor the control group had proliferative retinopathy, and all the studied sample showed only a non-proliferative type of retinopathy.

Retinopathy was more prevalent in patients with sickle cell disease (the three diseased groups collectively) 9 (15%) , than in control group 2 (3%), with P value <0.05 (Table II), however, there were no significant differences between patients with AS and SS type of hemoglobin on one hand and control group on the other hand (P>0.05). Nevertheless, patients with SF type of hemoglobin showed highly significant differences in the prevalence of retinopathy in comparison with the control group P < 0.001(Table III).

Retinopathy was more prevalent in males in the patient's group in comparison to the control group (P<0.05), furthermore it was more common in patients with SF hemoglobin, while it was statistically not significant in the other two diseased groups (AS and SS), and control (Table IV).

Table V showed the prevalence of retinopathy in those above and below 40 year of age in both studied groups. There was a statistically significant difference between the prevalence of retinopathy in patients above 40 year in comparison with those below 40 year, while no similar difference was found in control group in those above and below 40 year.

Discussion

Retinopathy is relatively a common problem in sickle cell disease[2,13,14], despite, we did not come across any study which determines the prevalence of retinopathy in sicklers in Iraq.

However, there are two main limitations of this study, first lacking the facility to do fluorescent angiography which is beneficial in detecting some form of retinopathy, second the inability to perform Hb variant and hence to diagnose Hb C which is considered as the most common type of hemoglobinopathy causing retinopathy[1, 2,15 -17].

The American Academy of Ophthalmology criteria for diagnosing and staging of retinopathy was followed[18], accordingly this study showed that retinopathy was more common in patients with sickle cell disease, 9(15%) ,in comparison to control group, 2(3%), this was statistically significant (P<0.05), and was consistent with many other relevant studies [8,9,11,16-18].

Our observation showed that retinopathy was solely of non-proliferative type, this in one hand might be explained by the unique genetic characteristic of our patients, on the other hand the inability to perform fluorescent angiography might be a cause of missing of some cases with proliferative retinopathy, nevertheless, Al-Salem[18] had failed also in detecting any proliferative retinopathy in his study.

Male patients showed more prevalence of retinopathy 7(77.6%), in comparison to females 2(22.4%), furthermore patients with SF type of hemoglobin had also a higher male prevalence, these results were consistent with other studies[19,20] which described a protective effect of estrogen in females from retinal ischemia .

Those who were above forty were significantly affected more than those below forty years 6(66.4%) and 3(33.6%) respectively, a result that matches other studies[21-24] this might be attributed to the ongoing process of sickling which had an additive effect on the retina that increased with age.

Retinopathy was significantly more prevalent in patient with SF type of hemoglbinopahty 5(55.5%), these findings were consistent with other studies [19,25-27] this can be explained by the increased viscosity of the blood in this type of hemoglobin resulting in more retinopathy[1,8,14,28].

Table I: Age and sex distribution of the studied sample.

Age group (years)	SS		AS		SF		AA	
	M	F	M	F	M	F	M	F
15-25	3	2	4	1	3	4	11	12
26-35	6	1	3	5	3	5	12	13
36-45	2	3	2	2	2	1	8	1
46-60	2	1	1	2	2	1	1	2
Total No.	13	17	10	10	9	11	32	28

Table II:Retinopathy & sex distribution among patients and controls.

Studied group	Male(%)	Female(%)	Total(%)
Patients (No.=60)	7(11)	2(3)	9(15)
Controls (No.=60)	1(1)	1(1)	2(3)

Table III:The prevalence of retinopathy in the three patient's groups and control.

	SS	AS	SF	*Total*
Patients (Retinopathy)	20(1)	20(3)	20(5)	60(9)
Control (Retinopathy)	60(2)	60(2)	60(2)	60(2)
P-Value	> 0.05	> 0.05	< 0.001	< 0.05

Table IV:Retinopathy and sex distribution among the three patient's groups and control.

Studied group	Total No.	Female (Retinopathy)	Male (Retinopathy)	P-Value
SS	20	7(1)	13(0)	> 0.05
AS	20	10(0)	10(3)	> 0.05
SF	20	11(1)	9(4)	< 0.05
Total No.	60	28(2)	32(7)	<0.05
Control(AA)	60	28(1)	32(1)	>0.05

Table V:The prevalence of retinopathy in those above and below 40 years.

Age	*Patients No.* *(Retinopathy)*	*Control No. (Retinopathy)*
> 40 year	26(6)	24(1)
< 40 year	34(3)	36(1)
P-Value	< 0.05	> 0.05

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