

Influence of α thalassaemia on the retinopathy of homozygous sickle cell disease

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Abstract

Homozygous α^+ thalassaemia (α^-/α^-) ameliorates some of the clinical manifestations of homozygous sickle cell (SS) disease but its effect on retinal complications remains unknown. This has been assessed by visual examination and fluorescein angiography in 39 subjects with SS disease and homozygous α^+ thalassaemia and in 39 age/sex matched controls with SS disease but with a normal α globin genotype ($\alpha\alpha/\alpha\alpha$). The results indicate that homozygous α^+ thalassaemia reduces the extent of peripheral retinal vessel closure but has no apparent effect on the frequency of proliferative sickle retinopathy.

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Normal people have four α globin genes, a pair of tightly linked α globin genes on each chromosome, and the genotype is depicted as $\alpha\alpha/\alpha\alpha$. Deletion of one of a pair of linked α globin genes results in a common form of α thalassaemia (α^+ thalassaemia or the α^- gene) which may be inherited from one ($\alpha^-/\alpha\alpha$) or both (α^-/α^-) parents. This abnormality occurs heterozygously in approximately 35% and homozygously in 3.5% of populations of West African origin and so frequently coincides with homozygous sickle cell (SS) disease. In SS disease, homozygous α^+ thalassaemia inhibits polymerisation of HbS reducing sickling, the haemolytic rate,¹ and some clinical manifestations of the disease.² There is evidence that it also inhibits vaso-occlusion of the peripheral retinal vasculature³ but its effect on proliferative sickle retinopathy (PSR) is unknown. Since homozygous α^+ thalassaemia results in a significantly higher haemoglobin level in SS disease² and since total haemoglobin is a risk factor for PSR in males,⁴ the prevalence of PSR might be expected to be increased. The influence of homozygous α^+ thalassaemia on peripheral retinal vessel occlusion and on the prevalence of PSR has therefore been assessed in SS subjects with homozygous α^+ thalassaemia ($SS\alpha^-/\alpha^-$) and in matched SS controls with a normal α globin gene number ($SS\alpha\alpha/\alpha\alpha$).

Patients and methods

The patients attended the sickle cell clinic of the University Hospital of the West Indies, Kingston, Jamaica. All patients with SS disease known to have homozygous α^+ thalassaemia aged 15 years and over ($n=49$) were requested to attend for detailed ophthalmic assessment during a 15 month study period (November 1987 to January 1989). Thirty nine (15 males, 24

females) responded and were matched by age and sex with 39 control SS patients with a normal α globin gene number by taking the individual closest in date of birth to the index case. Age matching was generally within 1 year in younger subjects and within 5 years in older subjects. The mean age of the study group was 30.4 years (range 15.7-65.3 years) and of the controls 30.2 years (15.3-67.8 years).

The diagnosis of SS disease was based on standard criteria⁵ and the α globin gene status established by restriction endonuclease analysis of DNA obtained from the buffy coat of peripheral blood.⁶

After obtaining informed consent, ocular examination was performed including corrected visual acuities, fundus examination through dilated pupils, fluoroscopy, and fluorescein angiography. Peripheral retinal vessel closure was detected on fluoroscopy and confirmed by angiography. The circumferential extent of closure was measured in 12 clock hours.

Results

VISUAL LOSS

Visual loss attributable to sickle retinopathy occurred in two eyes of two patients (one index, one control). A 17-year-old female patient with homozygous α^+ thalassaemia developed a vitreous haemorrhage from unilateral PSR which reduced acuity to 6/60 but cleared over 2 months to normal acuity. A 23-year-old female control had angiod streaks and a macular disciform scar which reduced acuity to counting fingers.

PERIPHERAL RETINAL VASCULAR CLOSURE

Fluoroscopy was performed on all but one subject (a 40-year-old female control known to have PSR) who had previously had an allergic reaction to fluorescein. The extent of closure was similar in both eyes of each subject so the scoring in each eye was combined for comparison between groups.

Peripheral retinal vessel closure was significantly less in patients with homozygous α^+ thalassaemia (mean 11.5 (SD 8.4)) than in controls (15.2 (SD 6.0)) (paired t test, $p=0.037$). The extent of closure was not significantly influenced by age in the index cases (correlation=0.30; $p=0.066$) or in controls (correlation=0.04, $p=0.82$). Closure tended to be more common in males, the mean difference being 2.9 hours in the index cases and 0.9 hours in the controls but neither difference reached significance (t test, $p=0.30$ and 0.67 respectively).

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PROLIFERATIVE RETINOPATHY

Proliferative retinopathy occurred in 7/39 (18%) patients with homozygous α^+ thalassaemia (three males, four females) and in 7/39 (18%) controls (five males, two females), the latter sex difference failing to reach significance. PSR was unilateral in four patients and bilateral in three in each group.

Patients with PSR tended to have more closure in both index cases and controls (Table 1) although only the difference in index cases with homozygous α^+ thalassaemia reached significance.

Discussion

There is debate in sickle cell disease as to whether peripheral retinal vessel closure is primarily a capillary event with secondary arteriolar closure or primarily an arteriolar closure with secondary capillary stasis and occlusion. Homozygous α^+ thalassaemia, from this report and from previous observations in a cohort study of sickle cell disease,³ is associated with significantly less peripheral retinal vessel occlusion. Homozygous α^+ thalassaemia has several effects on the haematology of SS disease.² Total haemoglobin is increased tending to raise whole blood viscosity and possibly compromise flow in arterioles but the mean reduction in cell haemoglobin concentration renders individual red cells more pliable, an effect likely to promote capillary flow. The reduction in peripheral retinal vessel occlusion in homozygous α thalassaemia is therefore more consistent with this occlusion being predominantly a capillary effect.

The extent of peripheral retinal vessel closure is believed to be one of the determinants of PSR formation and in both study and control groups, PSR affected cases tended to have more extensive closure, though this relationship only reached significance in subjects with homozygous α^+ thalassaemia. The lesser extent of closure in SS disease with homozygous α^+ thalassaemia might therefore have been expected to be reflected in a lower prevalence of PSR in this group. The equal

prevalence observed could be interpreted as a greater propensity for PSR formation, though this was not supported by the analysis which showed that those patients with homozygous α^+ thalassaemia developing PSR tended to have more extensive closure. The lesser vaso-occlusive severity of SS disease with homozygous α^+ thalassaemia may also render PSR lesion less prone to autofarction and therefore more likely to persist.

This would be consistent with previous reports of PSR in sickle cell disease showing that PSR tends to be more common in genotypes with less systemic vaso-occlusion. Thus the highest frequency of PSR occurs in sickle cell haemoglobin C (SC) disease⁷ which is usually associated with an otherwise benign clinical course. A hypothesis advanced to explain this apparent enigma suggests that PSR characterises subjects with a moderate vaso-occlusive tendency sufficient to induce peripheral retinal ischaemia and a stimulus to new vessel formation, but insufficient to occlude the new vessels formed. In patients with SS disease and a generally high vaso-occlusive tendency, retinal ischaemia develops but the new vessels are also spontaneously occluded inhibiting the development of PSR.

The interaction of homozygous α^+ thalassaemia with SS disease therefore represents a model consistent with the mild vaso-occlusive tendency seen in some mildly affected patients with SS disease and in most patients with SC disease. It also illustrates that modest reductions in intravascular sickling may not be universally beneficial and may actually increase some aspects of the pathology of sickle cell disease.

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Table 1 Extent of peripheral retinal vessel closure and presence of proliferative sickle retinopathy (PSR) in SS patients with homozygous α^+ thalassaemia (SS α^+ / α^+) and SS controls (SS $\alpha\alpha$ / $\alpha\alpha$)

Group	PSR negative			PSR positive			Significance* (p value)
	n	median	range	n	median	range	
SS $\alpha\alpha$ / $\alpha\alpha$	32	14	(2-24)	7	24	(11-24)	0.062
SS α^+ / α^+	32	11	(0-24)	7	24	(7-24)	0.0035

*Significance determined by Mann Whitney test.

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