Ocular findings in Saudi Arabian patients with sickle cell disease

Selwa Al-Hazzaa, Alan C Bird, Andreas Kulozik, Beryl E Serjeant, Graham R Serjeant, Peter Thomas, Andrew Padmos

Abstract

Aim—This study was set up to determine whether or not retinal changes occur in sickle cell disease in Saudi Arabian subjects with either the Benin, which exists in the south western part of the kingdom, or Asian haplotypes in the east, and to compare the findings with those in sickle cell disease in Jamaica.

Methods—Retinal examination and fluorescein angiography were performed in 61 patients with SS disease (40 eastern, 20 south western, 1 central region) and 10 with sickle cell βthalassaemia.

Results—Peripheral retinal vascular changes were common, and a qualitatively abnormal vascular border believed to imply risk of proliferative sickle retinopathy (PSR) was significantly more common in south western SS patients and PSR was shown in one of these. There were no differences in visual acuity, the presence of peripheral retinal patches, or the circumferential or posterior extent of peripheral retinal vessel closure between SS disease and sickle cell βthalassaemia or between SS disease in the two regions. Compared with the Jamaican Cohort Study, >180° of the peripheral retinal vasculature was seen significantly less frequent, suggesting factors inhibiting vascular remodelling in Saudi patients in early life.

Conclusion—Sickle cell disease in Saudi Arabia affects the retina and represents a potential threat to vision. Changes occur whatever the haplotype, and is similar to that observed in Jamaica.

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Sickle cell disease in Saudi Arabia presents interesting and instructive differences from that observed in populations of African origin. The mutation in the south west of the kingdom is of the Benin haplotype, is probably imported from Africa, and has similar levels of fetal haemoglobin (HbF) to those observed in African patients with the same haplotype. In the eastern province, there has probably been an independent mutation of the sickle cell gene, the so-called Asian haplotype, which is associated with higher levels of HbF. In both areas, the disease coincides with high frequencies of αthalassaemia. There are differences, and clinical features of SS disease between the two regions of Saudi Arabia which in the absence of obvious environmental differences, are presumed to reflect these genetic differences. There are no reports of retinal involvement in sickle cell disease in Saudi Arabia. Observations from general clinical features suggest that patients from the south west might have sickle cell retinopathy similar to that observed in patients of African origin, whereas those in the east with both high HbF levels and frequent αthalassaemia should be protected from vaso-occlusion and consequently show little retinal damage. The present study had two objectives: firstly, to learn whether sickle cell eye disease occurs in Saudi Arabia; and, secondly, to use the opportunity of the genetic and haematological diversity of Saudi patients with sickle cell disease, to learn more about the risk factors for retinal involvement.

Patients and methods

Patients
The patients attended the sickle cell clinic operated by the Department of Oncology at King Faisal Specialist Hospital, Riyadh, Saudi Arabia. This clinic serves patients resident in the Riyadh area but also conducts biannual assessments of patients from both the eastern and south western provinces where sickle cell disease is relatively common. The study was confined to patients showing only haemoglobins F, S, and A2 on haemoglobin electrophoresis—that is, homozygous sickle cell (SS) disease or sickle cell βthalassaemia (Sβthalassaemia), aged 17 years and above who had fluorescein angiography and angioscopy allowing description of the peripheral retinal vascular border. A total of 88 patients had been previously characterised and all were given appointments during a 5 day period in April 1993. Seventy four (84%) attended but three SS patients were excluded on the basis of penetrating ocular trauma (one), high myopia (one), and no veins for fluorescein angiography (one). The study group comprised 71 patients, 61 with SS disease (33 male) and 10 with Sβthalassaemia (five male). The patients were further divided according to geographical origin, 44 (40 SS, four Sβthalassaemia) originating in the eastern province, 25 (20 SS, five Sβthalassaemia) from the south west, and two (one SS, one Sβthalassaemia) from the central region. Data from these last two patients were used in the genotype comparison and haemoglobin electrophoresis were used to confirm these genotypes. The data were further used by the central region was excluded from the analyses comparing features of the eastern and south western regions.
The retinal vascular border as recorded by fluorescein angiography was graded according to a recent classification which appears to have prognostic significance. A type I border was qualitatively similar to normal with a smooth border formed of arteriovenous loops, the capillaries becoming longer and less densely packed as the border is approached. The border may differ from normal by being more posteriorly placed, and vascular anomalies internal to the border are more common than normal. A type II border is irregular, demonstrates a sharp demarcation between perfused and non-perfused retina with abrupt terminations of small or medium calibre vessels, and a dense capillary bed up to the margin of perfusion. This pattern was further subdivided into those manifesting capillary buds or stumps extending into non-perfused retina (type IIa) and those without (type IIb). In some angiograms, the border was unclassifiable either because it was too peripheral to photograph or the photographs were of poor quality. Examinations were performed by the two ophthalmologists (SH, AB) without knowledge of the geographical origin of the patients.

STASTICAL METHODS
The \( \chi^2 \) test for association was used for nominal variables when the numbers were large enough. When the variables were ordered, the association was further investigated using the \( \chi^2 \) test for trend. When expected frequencies were too small, the variables were regrouped to a 2 by 2 table, and the association tested using Fisher's exact test. Logistic regression was used when it was necessary to take other factors into account. Comparison of two means was made using the t test, with separate variance estimates when variances were not homogeneous. When there were more than two means, analysis of variance was used, with Bonferroni adjusted p values to test pairwise contrasts. The distribution of HbF was highly skewed and was transformed by \( \log_2 (\text{HbF}+1) \) before analysis.

Results
Retinal vascular changes were identified in this study which were similar qualitatively to those seen in the Jamaican cohort comprising fresh vascular obstruction (Fig 1), posterior displacement of the vascular border, and abnormalities of the peripheral vasculature (Figs 2 and 3).

COMPARISON OF SS DISEASE AND SICKLE CELL \( \beta^0 \) THALASSAEMIA
There were only 10 patients with sickle cell \( \beta^0 \) thalassaemia so data from eastern, south western, and central regions were pooled for comparison with SS disease. The number of \( \alpha \) globin genes (known in 53 SS, six \( \beta^0 \) thalassaemia) did not differ significantly between genotypes, there being 25 \( \alpha^+\alpha^+ \), 20 \( \alpha^-\alpha^- \), and eight \( \alpha^-\alpha^+ \) in SS disease.
Regional differences in haematology of SS disease

The number of α globin genes was known in 33 eastern and 19 south western subjects, there being eight homozygotes for α thalassaemia (α−/α−), 13 heterozygotes (α−/αα), and 12 with a normal α globin gene complement (αα/αα) in the east compared with 0, six, and 14 in the south west. The trend of an increasing east:west ratio with decreasing number of α globin genes was statistically significant (p<0·01). Total haemoglobin levels in eastern patients (mean 10·5, SD 1·5) were significantly higher than in the south west (9·4, 1·5) (t test, p=0·013). Fetal haemoglobin levels in eastern patients (median 12·0%, range 3·3–22·1) were also significantly higher than in the south west (median 4·44%, range 0·5–17·9) (t test on transformed data, loge (HbF+1), with separate variance estimates, p<0·001). Mean cell volume in the eastern patients (mean 83·0 fl, SD 11·1) was significantly lower than in south western patients (mean 89·7 fl, SD 10·4) (t test, p=0·03).

Regional differences in ophthalmology of SS disease

Visual acuity was <6/12 in seven (18%) eastern patients and in three (15%) of south western patients (p=1·00 using Fisher’s exact test). Acuity was <6/60 in three (4%) eyes of eastern subjects and in two (5%) eyes of south western subjects none of which was attributable to sickle cell disease. Patches occurred in the peripheral retina of 16 (40%) eastern patients and in 10 (50%) of south western patients, this difference not reaching significance (χ² test, p=0·65).

In all patients the peripheral border of retinal vascularity was seen, the circumferential extent being >180° in 20 (50%) eastern patients and in 12 (60%) south western subjects (χ² test, p=0·65). Total circumferential closure occurred bilaterally in 19 (48%), unilaterally in one eastern patient, and bilaterally in 12 (60%) south western patients. Posterior closure occurred in 11 (28%) eastern and in six (30%) south western patients, there being no regional difference (χ² test, p=1·00).

Classification of the retinal border on fluorescein angiography was possible in 71 (89%) eyes of eastern and in 38 (95%) eyes of south western patients (Table 1). Border type IIa was significantly more frequent in south western patients (Fisher’s exact test, p=0·03). Proliferative sickle retinopathy occurred in one subject, a 35-year-old man from the south west.

Eye variables and haematology

The regional differences in haematology imply that analysis of the relation between eye variables and haematology should take region into account using analysis of variance. Subjects with >180° of the anterior border seen had a lower HbF compared with those with ≤180° (Table 2). The relation between the extent of the border seen and α thalassaemia (heterozygous and homozygous forms combined) appeared to differ in the two
regions. There was no association in the eastern province, α thalassaemia occurring in 10/15 subjects with ≤180° compared with 11/18 subjects with >180° (p=1.00 using Fisher's exact test). In south western patients, α thalassaemia occurred in 0/7 with ≤180° and in 6/12 with >180° (Fisher's exact test, p=0.04), suggesting α thalassaemia as a risk factor for posterior displacement of the vascular border.

Table 1  Angiographic classification of the peripheral retinal vascular border in SS patients from the two regions of Saudi Arabia. Each eye is scored as to the most serious characteristic, and the summary score refers to a subject scored as to the eye with the most serious characteristic.

<table>
<thead>
<tr>
<th>Border type</th>
<th>Eastern region (%)</th>
<th>Western region (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left eye</td>
<td>Right eye</td>
</tr>
<tr>
<td>I</td>
<td>33 (87)</td>
<td>28 (85)</td>
</tr>
<tr>
<td>IIa</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>IIb</td>
<td>4 (11)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>33</td>
</tr>
</tbody>
</table>

COMPARISON WITH JAMAICAN DATA
When compared with subjects in the two regions of Saudi Arabia, Jamaican patients had significantly lower HbF (mean 7.9, SD 1.2) than either region, lower HbF (median 4.5, range 0.4–14.9) than eastern subjects only, similar mean cell volume values (mean 84.8, SD 8.9) to those of both regions and significantly less α thalassaemia (30 αα/αααα, 13 αα/αααα, 0 αα/αααα) than the eastern region.

The presence of patches (26 (43%) Saudi patients, 24 (59%) Jamaicans) and of posterior closure (17 (28%) Saudi patients, 14 (33%) Jamaican patients) did not differ between the groups (χ² test, p=0.19 and p=0.75 respectively). The proportion of patients with >180° of the circumference of the vascular border seen (32/60 Saudi patients, 39/42 Jamaican patients) was significantly greater in Jamaicans (p<0.001 using χ² test). Comparison of angiographic border type showed that type IIa was significantly more common in south western patients (5/19) than in Jamaicans (1/36) (Fisher’s exact test, p=0.03), there being no difference between eastern Saudi patients and Jamaicans (Fisher’s exact test, p=1.00).

Discussion
Despite the small number of patients in this study it is clear that SS disease in Saudi Arabia is associated with peripheral retinal vessel changes which are similar to those seen in the subjects of African origin. The finding that 10 (14%) of patients had sickle cell b° thalassaemia among 71 subjects with an SS phenotype, suggests a greater relative frequency of this genotype than occurs in populations of African origin. The retinal involvement in sickle cell b° thalassaemia was similar to that in SS disease although no patients with Sb° thalassaemia had a type II border in this study.

It was of interest to assess whether retinal vascular involvement differed between the two regions since the Benin haplotype occurs in the south west and the Asian haplotype accounts almost exclusively for the disease in the eastern province, and eastern patients showed a greater frequency of α thalassaemia than either region. There was no effect of frequency of the eastern region in the regression analysis.

Table 2  Relation between ocular findings (≠180° of the vascular border seen, presence of patches, posterior position of the vascular border, and border classified as II) and age and haematological indices

<table>
<thead>
<tr>
<th>Age</th>
<th>Hb</th>
<th>log10 (Hb+1)</th>
<th>MCV</th>
<th>Adjusted odds ratio (95% CI) for α thalassaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular border seen</td>
<td>-0.9 (4.3, 2.4)</td>
<td>-0.1 (0.9, 0.7)</td>
<td>-3.2 (2.8, 2.5)</td>
<td>See text</td>
</tr>
<tr>
<td>Patches</td>
<td>-2.2 (5.5, 1.2)</td>
<td>-0.2 (1.0, 0.6)</td>
<td>-7.5 (2.9, 2.1)</td>
<td>2.6 (0.7, 9.1)</td>
</tr>
<tr>
<td>Posterior border</td>
<td>-0.4 (4.1, 3.4)</td>
<td>0 (2.1, 0.2)</td>
<td>2 (1.0, 3.8)</td>
<td></td>
</tr>
<tr>
<td>Border classification</td>
<td>0 (0.4, 3.9)</td>
<td>-0.3 (3.1)</td>
<td>2.5 (4.4, 4.9)</td>
<td>1 (0.3, 5.1)</td>
</tr>
</tbody>
</table>

* Variance differed between regions so regions presented separately. MCV = mean cell volume.
Comparison with the Jamaican cohort study should be treated with caution because of the difference in mean ages (27-7 years for Saudi patients, 17-8 years for Jamaicans), and the Saudi patients were not derived from unselected population base. In Jamaican subjects the extent of vascular border seen was greater, despite their younger mean age, suggesting a factor inhibiting vessel closure in both regions of Saudi Arabia in early life. This factor is unlikely to be the frequency of high HbF levels or a thalassaemia since these did not differ between south western Saudi and Jamaican patients. Furthermore, the type Ila border was more common in south western than Jamaican patients, possibly reflecting the greater mean age of south western Saudi patients, a specific risk factor, or the symptomatic bias inherent in patients attending a tertiary referral hospital. The greater prevalence of an unstable type Ila border may be relevant for visual prognosis since this border implies threat of PSR which may in turn lead to visual loss. By contrast, a type I border, however posteriorly placed, is not followed by this complication and may be protective of proliferative disease.

Overall, despite minor differences, the ocular pathology in SS patients from each region of Saudi Arabia and differed little from that observed in Jamaicans with SS disease. That this is the case despite differences in haematological variables and clinical features should not be surprising, since visually threatening retinal vascular disease is seen most commonly in forms of sickle cell disease which may otherwise be relatively mild. Although no case in this study had lost vision as a consequence of their haemoglobinopathy, the number of cases was small, and it is likely that SS disease represents a threat to vision in Saudi Arabia albeit small. The more florid retinal pathology often observed in Jamaican patients is generally attributable to sickle cell haemoglobin C (SC) disease or sickle cell β thalassaemia which were not encountered in Saudi Arabia.

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