Transient open-angle glaucoma associated with sickle cell trait: report of 4 cases

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SUMMARY Four black patients, all with sickle trait (SA), developed transient open-angle glaucoma with blood in Schlemm's canal. In 3 patients the condition followed blunt trauma, while in the fourth no antecedent trauma was described. The intraocular pressure became normal in all 4 cases with the resolution of the haemorrhage from the trabecular meshwork and Schlemm's canal.

Sickle cell trait, the commonest of the sickle haemoglobinopathies, affects approximately 9% of the black population of North America.1 A variety of ocular abnormalities2-11 have been reported to occur in patients with sickle cell trait. These have included proliferative retinopathy, chorioretinal scarring, spontaneous vitreous haemorrhages, central retinal vein occlusion, angioid streaks, conjunctival vascular abnormalities, and transient open-angle glaucoma. We herewith report 4 additional cases of transient open-angle glaucoma which occurred in patients with sickle trait. In 3 patients the glaucoma followed blunt trauma with microscopic hyphaema, while in the fourth patient a microscopic haemorrhage appeared in Schlemm's canal spontaneously. All patients had blood in the trabecular meshwork or the canal of Schlemm on gonioscopy, and the glaucoma resolved concomitantly with clearing of blood from these areas.

Case reports

Case 1
A 53-year-old black woman had a history of 3 episodes of blurred vision in the right eye associated with halos at lights for a 4-week period. These episodes lasted several hours each and were not accompanied by pain, injection, or other ocular symptoms. The patient had hypertension of 8 years' duration, treated with methyldopa and a diuretic, and rheumatoid arthritis for several years, treated with compound aspirin, phenacetin and caffeine tablets. There was no history of diabetes mellitus, glaucoma, ocular trauma, or other medical or ocular diseases. An ophthalmological examination 1½ years previously showed a corrected visual acuity of 20/25 in each eye, applanation tension of 22 mmHg OU and a cup/disc ratio of 0·25 in each eye.

Ophthalmological examination during the present illness revealed a corrected visual acuity of 20/30 OU. Applanation pressures were 42 mmHg OD and 10 mmHg OS. Slit-lamp examination of the anterior segment was normal in both eyes. Gonioscopic examination of the anterior chamber angle showed a grade III-IV open angle in both eyes, without recession or neovascularisation. However, the right eye showed blood present in Schlemm's canal (7.00 to 11.00 o'clock), and a haemorrhage localised to the trabecular meshwork from 7.00 to 8.00 o'clock (Fig. 1). On ophthalmoscopic examination cup/disc ratios of 0·45 OD and 0·15 OS were seen on stereoscopic examination at the slit-lamp. Outflow facilities were 0·14 OD and 0·21 OS. Goldmann kinetic perimetry was normal in both eyes. Systemic blood pressure was 190 mmHg systolic and 110 mmHg diastolic.

A complete blood count and sedimentation rate were normal. Antinuclear antibody and latex fixation tests were negative. Haemoglobin electrophoresis revealed an AS pattern. The 3-hour oral glucose tolerance test was abnormal: fasting blood sugar 117 mg/100 ml (6·5 mmol/l); at 1 hour 231 mg/100 ml (12·8 mmol/l); at 2 hours 166 mg/100 ml (9·2 mmol/l); at 3 hours 88 mg/100 ml (4·9 mmol/l).

The patient was treated with acetazolamide
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Fig. 1 Goniophotograph of case 1 showing blood in the canal of Schlemm.

Fig. 2 Goniophotograph of case 3 showing blood in the trabecular meshwork.

250 mg orally 4 times a day and Epitrate (adrenaline acid tartrate) drops 2% OD twice a day. Over a 2-week period the trabecular haemorrhage and blood in Schlemm's canal resolved. The intraocular pressure remained normal after medication was discontinued and remained normal when the patient was last examined 18 months later.

CASE 2
A 9-year-old boy was struck in the left eye with a stick 24 hours before admission to hospital. He immediately developed a reduction in vision followed several hours later by pain in the eye and vomiting. Ocular examination showed the uncorrected visual acuity to be 20/20 OD and 20/200 OS. Applanation pressures were 10 mmHg OD and 40 mmHg OS. A superficial abrasion was present on the left upper eyelid. The left eye displayed moderate conjunctival hyperaemia and mild microcystic corneal epithelial oedema. The anterior chamber of the right eye was clear while the left eye had 3+ flare and cells (many erythrocytes). No gross hyphaema was seen at the
slit-lamp. The pupillary reflex was brisk OD and sluggish OS. The vitreous and fundus were unremarkable. Gonioscopy of the left eye revealed blood in Schlemm’s canal.

The patient was placed on bed rest, sedation, and acetazolamide 125 mg by mouth 4 times daily. Examination next day showed an uncorrected visual acuity in the left eye of 20/20 with intraocular tension 36 mmHg. Gonioscopy showed blood layered in the inferior portion of the anterior chamber angle and prominently in Schlemm’s canal in the remainder of the angle. A sickle preparation was positive, and haemoglobin electrophoresis revealed an AS pattern (Hgb A 56%, Hgb S 44%). All other laboratory tests including complete blood count, urine analysis, sequential multiple analyser (SMA) 6 and 12 were normal. The haemorrhage cleared from the anterior chamber over the next 5 days with return of intraocular pressure to normal levels. The acetazolamide was discontinued without sequelae. The patient was asymptomatic when examined 24 months later.

CASE 3
A 23-year-old black man was struck in the right eye. He noticed a mild decrease in vision with pain in the eye. He was in excellent health otherwise. Ophthalmological evaluation showed a best visual acuity of 20/50 OD and 20/20 OS. The left eye was completely normal. Applanation pressures were 30 mmHg OD and 14 mmHg OS. The right eye had 2+ bulbar hyperaemia, clear cornea with very fine cellular deposits on the endothelium, 3+ aqueous flare, and cells (mostly erythrocytes). Gonioscopy revealed a grade 3 open angle OU with a dark red band of blood in the trabecular meshwork OD (Fig. 2). No peripheral anterior synechiae or recession of the anterior chamber angle were present. The pupillary reactions, lens, vitreous, and fundus were normal. Tonography at this time revealed a facility of outflow of 0-08 OD and 0-26 OS. The patient was put on acetazolamide 250 mg by mouth 4 times daily and prednisolone acetate 1% eye drops 4 times daily.

Haemoglobin electrophoresis revealed an AS pattern (Hgb A 55%, Hgb S 45%). All other laboratory studies, including complete blood count, urine analysis, SMA 6 and 12, and serum electrophoresis were within normal limits.

The blood cleared from Schlemm’s canal 1 week after admission with a concomitant return of intraocular tension to 16 mmHg. The visual acuity returned to 20/20, but a repeat tonography showed a coefficient of outflow of 0-14 OD and 0-24 OS. Visual fields with tangent screen utilising a 3 mm white target at 1 m were normal in each eye. All medications were discontinued. The patient was discharged and lost to follow-up.

CASE 4
The patient was a 34-year-old black man who was punched in the left eye. When seen 2 days later the corrected visual acuity was 20/20 OD and 20/100 OS. Intraocular pressure was 16 mmHg OD and 36 mmHg OS. The right eye was entirely normal. The left eye displayed 2+ bulbar hyperaemia and moderate microcystic corneal oedema. The cornea was cleared with topical glycerin. No keratic precipitates were present. The anterior chamber revealed 2+ aqueous flare and cells, many of which were erythrocytes. Gonioscopy showed a grade 3 open angle, both eyes, and in the left eye a dense column of dark red blood in Schlemm’s canal. The pupillary reactions were brisk OD and sluggish OS. The lens, vitreous, and fundus appeared normal. The patient was placed on acetazolamide 250 mg by mouth 4 times daily and prednisolone acetate 1% drops 4 times daily. A complete laboratory examination and haemoglobin electrophoresis revealed AS pattern (Hgb A 59%, Hgb S 41%). The intraocular tension was unchanged over the next 24 hours, and consequently the patient was given oral glycerol 1-5 mg per kg. After 2 hours, the intraocular pressure was 22 mgHg in the left eye. Acetazolamide and glycerol were both required to control the intraocular tension for the ensuing 6 days. Examination at that time showed an intraocular pressure of 24 mmHg and blood in Schlemm’s canal. Glycerol was discontinued. Visual fields utilising a tangent screen at 1 m with a 2 mm white target were full in both eyes. Tonography revealed a facility of outflow of 0-22 OD and 0-10 OS. During the next 10 days the blood in Schlemm’s canal was gradually absorbed and the intraocular pressure was 16 mmHg. Tonography at that time was 0-20 OD and 0-20 OS. Ocular examination 18 months later was entirely within normal limits.

Discussion
The severity of symptoms in patients with sickle-cell trait depends on several factors any of which may increase the amount of sickling. These factors are: the percentage of S haemoglobin, oxygen tension, pH, temperature, viscosity, vascular stasis, hyperkalaemia, increased carbon dioxide level, and presence of reducing substances. Thus, as Shapiro and Baum observed, the consequence of small nontraumatic (case 1) or traumatic haemorrhages (cases 2, 3, 4) in a patient may be transient open-angle glaucoma due to the incarceration of sickled erythrocytes in the canal of Schlemm and trabecular meshwork.

An erythrocyte can pass through vessels smaller than its own diameter because of its ability to alter
its own discoid shape. Thus the case with which normal erythrocytes can negotiate the pathways through the trabecular meshwork, juxtaocular tissue, and into Schlemm's canal depends on their extreme plasticity and easy deformability. Inomata and associates\textsuperscript{14} showed in the cynomolgus monkey that normal erythrocytes measuring approximately 6–7 $\mu$m in diameter could pass through the endothelial trabeculae and enter the vacuoles of endothelial cells through 2.5–3.5 $\mu$m pores by virtue of the erythrocyte's pliability. Erythrocytes then pass from the vacuoles into the canal of Schlemm through pores 1.0–1.8 $\mu$m in diameter. Erythrocytes can also pass through short pores 1.0 $\mu$m in diameter in the flat portion of the trabecular endothelium into the canal. In sickled erythrocytes\textsuperscript{13} the haemoglobin becomes relatively insoluble and aggregates into long polymers possessing a tubelike structure 20–22 nm in diameter. Sickled erythrocytes are rigid and nonpliable and cannot pass through the trabecular meshwork. Reduced erythrocyte deformability has also been observed in thalassaemia spherocytosis and, recently, in diabetes mellitus.\textsuperscript{15}

Presumably increased haemoglobin A$_{1c}$ (Hb A$_{1c}$) formed by the glycosylation of haemoglobin causes an increased intracellular viscosity and a concomitant decreased erythrocyte deformability.\textsuperscript{16} Goldberg\textsuperscript{17} in his study of 3 patients with sickle-cell trait who sustained traumatic hyphaemas found that they had more sickling of erythrocytes in their aqueous than in their peripheral venous blood. In consonance with variations in haemoglobin S concentration in patients with sickle trait Goldberg\textsuperscript{17} observed that a lower percentage of sickled erythrocytes was found in the aqueous of the patients with lower concentration of haemoglobin S. This observation is supported by studies on the inhibitory effect of deoxygenated normal haemoglobins (A or F) on the polymerisation of deoxygenated haemoglobin S.\textsuperscript{13} In all our cases it would be difficult on the basis of clinical examination to determine the exact site(s) of entrapment of deformed erythrocytes.

Patient 1 was at first thought to have had a glaucomatocyclitic crisis because of the recurrent blurring of vision, painless elevation of intraocular pressure, a white eye, open angles, normal visual fields, and intraocular pressure between attacks.\textsuperscript{18} The mild ocular hypertension (22mgHg OU) noted before the attacks and the cup/disc asymmetry are unusual in this entity, although a predilection for glaucomatocyclitic crisis in patients with primary open-angle glaucoma has been suggested.\textsuperscript{19} The lack of evidence of anterior chamber inflammation in this patient on every examination, the persistence of blood in the trabecular meshwork or in Schlemm's canal, and the trabecular meshwork haemorrhage are all atypical for glaucomatocyclitic crisis and make this diagnosis untenable.

Boniuk and Burton\textsuperscript{10} reported 2 cases of unilateral glaucoma associated with sickle cell retinopathy. They postulated that the glaucoma was secondary to neovascularisation and peripheral anterior synechiae within the chamber angle which developed as a sequel to intravascular sickling. None of our patients had sickle retinopathy, neovascularisation, or peripheral anterior synechiae.

Haemorrhage into the trabecular meshwork is an uncommon occurrence. Amsler and Verrey reported observing a haemorrhage in the anterior chamber angle following paracentesis in Fuchs's heterochromic iridocyclitis and considered it to be characteristic.\textsuperscript{21} Haemorrhage from Schlemm's canal has been reported to have been induced by gonioscopy in these patients\textsuperscript{22 23} and in a few normal and glaucomatous eyes.\textsuperscript{24} However, none of our patients had heterochromia iridis, as is typically seen in Fuchs's iridocyclitis.\textsuperscript{25 26} Trabecular haemorrhage has also been observed in severe iridocyclitis,\textsuperscript{27} but none of our patients had evidence of severe ocular inflammation.

The spontaneous reflux of blood into Schlemm's canal may occasionally be seen in conditions that produce ocular hypotony or raised episcleral venous pressure.\textsuperscript{28} Increased episcleral venous pressure may be produced by gonioscopy and by inflating a blood pressure cuff about the neck. Either manoeuvre may produce obstruction of blood flow through the jugular veins. Sickle-cell disease, hypertension, rheumatoid arthritis, and diabetes mellitus are all associated with small-vessel disease, which may be associated with episcleral venous obstruction and stasis and lead to sickling of blood that has spontaneously refluxed into Schlemm's canal. Cogan and coworkers reported that in diabetes mellitus patients may have an elevated serum viscosity.\textsuperscript{29} Coupled with an increased intracellular viscosity due to glycosylation and decreased erythrocyte deformability,\textsuperscript{15 16} these may also predispose to venous stasis and sickling.

The treatment of what may hitherto have been described as 'insignificant' hyphaemas in blacks must be re-evaluated. All blacks with hyphaemas should have sickle screening tests and haemoglobin electrophoresis. Because of the effects of increased intraocular pressure in reducing perfusion to the retina and optic nerve in patients with sickle trait, extreme care must be undertaken in monitoring the intraocular pressure.\textsuperscript{7 9} The ophthalmologist must be judicious in the use of carbonic anhydrase inhibitors and osmotic therapy. Increased serum tonicity due diuretic and osmotic therapy in association with vascular stasis coincident with increased
intraocular pressure may precipitate vascular occlusions in patients with sickle-cell trait. And, as Goldberg has suggested, early anterior chamber paracentesis may be the most efficacious method of removing sickled erythrocytes from the anterior chamber.

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