Outcome of iatrogenic choroidal neovascularisation in sickle cell disease

Peter D Fox, Robert W Acheson, Graham R Serjeant

Abstract

Choroidal neovascularisation developed in 62/66 (94%) eyes followed up for a mean period of 11.2 years after treatment with xenon arc feeder vessel coagulation for proliferative sickle retinopathy (PSR). In 27 eyes the neovascularisation was chorioretinal alone and in 35 eyes chorioretinal. Chorioretinal neovascularisation (CRN) was a benign complication but may convert to chorioretinal neovascularisation (CVN). Late sequelae of CVN included vitreous haemorrhage, posterior vitreous face fibrosis, and tractional retinal detachment. Visual loss (of ≥ 3 Snellen lines for ≥ 3 months) occurred in nine eyes affected by choroidal neovascularisation, though because of other pathology this could not always be attributed to the choroidal neovascularisation. The incidence of visual loss in CVN affected eyes was significantly greater, by survival curve analysis, than in eyes affected by CRN alone. Permanent visual loss from tractional retinal detachment definitely attributable to CVN occurred in 2/35 (6%) eyes.

Treatment of proliferative sickle retinopathy (PSR) by feeder vessel coagulation achieves closure of the new vessels in most patients.¹ Choroidal neovascularisation at the coagulation site is a serious complication of feeder vessel treatment because of the risk of subsequent vitreous haemorrhage or retinal traction.^{2,3} However, the long term risk to visual function is unknown, and the experience with iatrogenic choroidal neovascularisation in 62 affected eyes monitored for a mean period of 11.2 years is therefore reported.

Patients and methods

Patients treated were in two consecutive trials of xenon arc feeder vessel coagulation of proliferative sickle retinopathy at the Sickle Cell Clinic, University of the West Indies, and were invited to attend for further review. They were enrolled between March 1973 and January 1977 in a non-randomised trial⁴ which assessed coagulation of both the feeding arteriole and the new vessels, and in a controlled randomised trial⁵ between April 1978 and September 1980 of coagulation of the feeding arteriole only. Of the 103 treated patients 29 were known to have emigrated, four had died, and 13 could not be traced. In the remaining 57 patients who attended for review there were 66 treated eyes of which 31 were treated in the first trial and 35 in the second. There were 40 patients with sickle cell-haemoglobin C (SC) disease, 12 with homozygous sickle cell (SS) disease, three with sickle

cell-beta⁺ thalassaemia, and two with sickle cell-beta⁰ thalassaemia.

The most recent assessment in 1988 included ocular symptoms, corrected acuities, fundal examination, and fluorescein angiography. The previous notes and angiograms were reviewed to determine the type, onset, and behaviour of any choroidal neovascularisation. These abnormal vessels may remain in the plane of the chorioretinal scar (CRN) or may extend into the vitreous (CVN). The mean follow-up of all 66 eyes from initial treatment until review in 1988 or until an eye had no perception of light was 11.2 years (range 7.5 to 15.4 years, except for one eye which had reached no perception of light after 3.2 years' follow-up). Visual loss was defined as a decrease in acuity of 3 or more Snellen lines for three or more months (using Snellen lines 6/6, 6/9, 6/12, 6/18, 6/24, 6/36, 6/60).

Results

Choroidal neovascularisation developed in 62/66 treated eyes (94%). CRN alone developed in 27 eyes and both CVN and CRN in 35 eyes. A total of 173 CRN lesions were identified in 62 eyes (range 1-6 per eye) and 70 CVN lesions in 35 eyes (range 1-4 per eye, involving 10-120° circumferentially).

Age, sex, genotype, and trial protocol did not influence the type of choroidal neovascularisation that developed, and no features distinguished the four eyes that did not develop choroidal neovascularisation. The mean age of all patients at initial treatment was 33.8 years (range 13.2-67.1 years).

Nine patients received bilateral treatment, of whom eight developed choroidal neovascularisation (unilateral CVN in one, bilateral CRN in two, bilateral CVN in two, and CRN in one eye and CVN in the other in three patients).

OPHTHALMOSCOPIC AND ANGIOGRAPHIC APPEARANCES

On ophthalmoscopy CRN appeared as a dirty white membrane within a coagulation scar and was usually surrounded by hyperpigmentation. CVN was whiter, more fibrous, and extended up in to the vitreous, often overlying anterior untreated retina.

On fluorescein angiography of CRN a fine vessel system could often be identified in early phases of the study (Fig 1A), but the characteristic finding was of hyperfluorescence confined to the coagulation scar in later phases of the study (Fig 1B). CVN usually showed a typical arborising pattern in early phases of the angiogram (Fig 2A) which leaked profusely in later phases

Medical Research Council Laboratories (Jamaica), University of the West Indies, Mona, Kingston 7, Jamaica
P D Fox
R W Acheson
G R Serjeant

Correspondence to: Professor G R Serjeant, Medical Research Council Laboratories, University of the West Indies, Kingston 7, Jamaica, West Indies.

Accepted for publication 26 January 1990

Figure 1: Superotemporal region of left eye in a 21-year-old female with SC disease with chorioretinal neovascularisation developing 1–18 months after treatment. (A) Early phase. (B) Late phase.

Figure 1A

Figure 1B

of the study (Fig 2B). The CVN feeding vessels usually passed through an area of CRN.

ONSET AND FOLLOW-UP OF CHOROIDAL NEOVASCULARISATION

The mean time interval between treatment and diagnosis was 1.3 years for CRN (in all 62 eyes developing choroidal neovascularisation) and 3.8 years for CVN. Chorioretinal neovascularisation was observed within one year of treatment in 37/62 eyes (60%) and within 35 days in one eye. Choriovitreous neovascularisation developed in 6/35 eyes (17%) in the first year and was first observed at 60 days in one eye. Most CVN developed between one and three years after treatment, though the observed interval was up to 7.8 years. The mean follow-up from the diagnosis of choroidal neovascularisation to last assessment was 9.9 years for CRN and 7.4 years for CVN.

GROWTH AND REGRESSION

Of the 173 CRN lesions identified in 62 eyes 25 (in 16 eyes) were CRN/CVN complexes when first observed. During follow-up a further 41 CRN lesions (in 25 eyes) converted into CRN/CVN complexes, of which one followed xenon

arc photocoagulation of a CRN lesion. Only four CVN lesions (in four eyes) did not have identifiable associated CRN. Of the 70 CVN lesions (in 35 eyes) angiograms adequate to assess behaviour were available for 57 lesions (in 30 eyes), of which 15 (in 10 eyes) enlarged 11 (in 9 eyes) regressed, nine (in 6 eyes) initially grew and later regressed, and 18 (in 13 eyes) remained stable on follow-up. There was no difference in length of follow-up of lesions manifesting growth, regression or stability. Xenon arc photocoagulation of the remaining four CVN lesions in three eyes (misdiagnosed as PSR) resulted in non-perfusion of all four, but subsequently three became reperfused and one remained non-perfused 7.2 years later. Growth of CVN lesions (Figs 3A, B) usually occurred in the two years following diagnosis, though it did occur between 5.8 and 6.3 years later in one lesion. Of the 20 CVN lesions showing spontaneous regression, this proceeded to non-perfusion in seven CVN lesions over intervals of 1.6–5.7 years from diagnosis, and haemorrhage into the CVN preceded regression in four lesions.

VITREOUS HAEMORRHAGE

Vitreous haemorrhage occurred in 19 eyes and

Figure 2: Superotemporal region of right eye in a 32-year-old female with SS disease with choriovitreous neovascularisation developing 19–24 months after treatment. (A) Early phase. (B) Late phase.

Figure 2A

Figure 2B

Figure 3: Superior region of right eye in a 43-year-old male with SC disease with choriovitreal neovascularisation 3·4 years after treatment. (A) One year after diagnosis of CVN. (B) One year later showing spontaneous growth.

Figure 3A

Figure 3B

could be traced to CVN in 14 eyes and to PSR in three. The remaining two eyes had both CVN and PSR, either of which could have been the source. Vitreous haemorrhage was recurrent in 8/14 CVN eyes. Haemorrhage sufficient to cause visual loss occurred in only four eyes (three with CVN, one with both CVN and PSR) and occurred 1·6–11·9 years after treatment. Vitreous haemorrhage not affecting vision occurred up to 15 years from treatment. No vitreous haemorrhages were associated with CRN.

RETINAL DETACHMENT

In 11 eyes with CVN and one eye with both CVN and PSR the detached or partially detached posterior vitreous face was fibrosed with peripheral attachments to neovascular tissue. Contraction of the posterior vitreous face led to tractional retinal detachments in three eyes with CVN and one eye with both CVN and PSR. Of the three CVN eyes with tractional detachments two lost vision 7·7 years and 13·4 years after treatment, and the third had a localised rhegmatogenous retinal detachment adjacent to CVN tissue as well as a localised posterior pole tractional detachment not affecting vision. The eye with both CVN and PSR developed a tractional detachment with visual loss at 9·2 years.

VISUAL LOSS

Visual loss occurred in nine eyes during the study (Table I). In one eye (case 6) a tractional detachment was preceded by vitreous haemorrhage

causing visual loss. In case 8, with both CVN and PSR, the eye became phthisical before ultrasound examination was available, so the presence of a detachment could not be ascertained. Irretrievable visual loss from tractional retinal detachments solely attributable to CVN occurred in two eyes (cases 6 and 7). The incidence of visual loss in eyes with only CRN was 0·3/100 eye years of observation after treatment compared with 2·2/100 eye years of observation in eyes with CVN (including eyes with both CVN and PSR). This difference was significant by survival curve analysis ($\chi^2=4\cdot17$, $p=0\cdot04$). Since CRNs and CVNs develop at different intervals after treatment, reassessments of these incidence rates for the known duration of choroidal neovascularisation gave corresponding figures of 0·4 and 3·1, representing an even greater difference.

Discussion

Choroidal neovascularisation was a common complication of feeder vessel coagulation of proliferative sickle retinopathy, and although occurring more frequently with xenon arc, occurs also with argon laser photocoagulation.^{5·6} Choroidal neovascularisation has followed xenon arc and argon laser photocoagulation in diabetic retinopathy⁷ usually when new vessels were repeatedly treated by focal photocoagulation using small spot sizes. Choroidal neovascularisation has also been induced by small, intense photocoagulation burns in rhesus monkeys,⁸ and histological examination confirmed vasoproliferation through defects in Bruch's membrane. Retinal ischaemia, choroidal ischaemia, and post-photocoagulation inflammation have all been postulated³ as stimuli for choroidal neovascularisation in sickle cell retinopathy following disruption of Bruch's membrane by photocoagulation. Since the frequency of choroidal neovascularisation did not differ between the two therapeutic protocols employed in the Jamaican studies, it seems unlikely that the more extensive photocoagulation in the first trial was a causal factor.

The development of choroidal neovascularisation in the great majority of patients receiving feeder vessel coagulation for PSR has raised the

TABLE I Visual loss in eyes with choroidal neovascularisation

Case	Age at treatment (years)	Sex and genotype	Visual loss (years)	Treatment to Visual acuity			Cause of visual loss	Type of new vessels
				Initial	Worst	Final		
1	48	M SC	6·7	6/6	2/60	2/60	Epiretinal membrane	CRN
2	51	M SC	9·6	6/6	6/36	6/36	Epiretinal membrane	CVN
3	28	F SC	12·0	6/6	6/60	6/60	Epiretinal membrane	CVN
4	32	M SC	11·9	6/6	HM	6/12	Vitreous haemorrhage	CVN
5	57	F SC	1·6	6/12	6/60	6/12	Vitreous haemorrhage	CVN
6	38	F SC	9·4	6/6	6/60	6/60	Vitreous haemorrhage	CVN
			13·4		NPL	NPL	Tractional detachment	
7	37	M SC	7·7	6/6	6/60	6/60	Tractional detachment	CVN
8	22	M SC	3·2	6/6	NPL	NPL	Vitreous haemorrhage	CVN and PSR
9	44	F SC	9·2	6/6	NPL	NPL	Tractional detachment	CVN and PSR

HM=hand movement. NPL=no perception of light.

concern that one neovascular network has been replaced by another which may have an equally bad or possibly worse visual prognosis. Complications from choroidal neovascularisation in sickle cell disease include vitreous haemorrhage, vitreoretinal traction, and tractional retinal detachments,^{2,3,9} but the long term risk to visual function remained to be determined. Earlier reports describing short term follow-up were contradictory. In 16 eyes developing CVN, followed up at this unit² for a mean period of 3.3 years, increasing retinal traction was observed in one eye, but there was no visual loss. In Chicago³ 10 eyes developed CVN following argon laser feeder vessel coagulation of PSR, and during a mean follow-up of 4.2 years three developed tractional retinal detachments, two of which involved the macula. However, the same group⁹ later described nine eyes with CVN over a mean follow-up of 5.8 years and found no permanent profound visual loss.

Longer term follow-up in the present study indicates that CRN was a benign complication, though conversion to CVN occurred in 41 lesions occasionally several years later. Vitreous haemorrhage from a CVN was common and often recurrent, but visual loss was unusual. Posterior vitreous face fibrosis attached to CVN was a more ominous sign, and progression to tractional retinal detachment and irretrievable visual loss were observed. Visual loss from macular epiretinal membranes was difficult to attribute to CRN or CVN because the complication may follow photocoagulation, vitreous haemorrhage, and PSR itself.¹⁰ The risk of visual loss in the present study was significantly greater in eyes developing CVN than CRN, and the

incidence rate of visual loss in CVN eyes was similar to that observed in untreated eyes with PSR in this unit.¹¹

This observation indicates that little has been achieved by the treatment of PSR if choriovitreous neovascularisation develops as a complication. Although it is commoner after xenon arc therapy, this complication also occurs with argon laser photocoagulation, and protocols for treatment by both methods should be changed so as to minimise the risks of development of choroidal neovascularisation.

- 1 Condon PI, Serjeant GR. Photocoagulation and diathermy in the treatment of proliferative sickle retinopathy. *Br J Ophthalmol* 1974; 58: 650-62.
- 2 Condon PI, Jampol LM, Ford SM, Serjeant GR. Choroidal neovascularisation induced by photocoagulation in sickle cell disease. *Br J Ophthalmol* 1981; 65: 192-7.
- 3 Dizon-Moore RV, Jampol LM, Goldberg MF. Choriovitreous and choriovitreous neovascularization. *Arch Ophthalmol* 1981; 99: 842-9.
- 4 Condon PI, Serjeant GR. Photocoagulation in proliferative sickle retinopathy: results of a five-year study. *Br J Ophthalmol* 1980; 64: 832-40.
- 5 Jampol LM, Condon PI, Farber MD, Rabb M, Ford SM, Serjeant GR. A randomised clinical trial of feeder vessel photocoagulation of proliferative sickle cell retinopathy: 1. Preliminary results. *Ophthalmology* 1983; 90: 540-5.
- 6 Condon PI, Jampol LM, Farber MD, Rabb M, Serjeant GR. A randomised clinical trial of feeder vessel photocoagulation of proliferative sickle cell retinopathy. II. Update and analysis of risk factors. *Ophthalmology* 1984; 91: 1496-8.
- 7 Chandra SR, Bresnick GH, Davis MD, Miller SA, Myers F. Choroidovitreous neovascular ingrowth after photocoagulation for proliferative diabetic retinopathy. *Arch Ophthalmol* 1980; 98: 1593-9.
- 8 Archer DB, Gardiner TA. Morphologic, fluorescein angiographic and light microscopic features of experimental choroidal neovascularization. *Am J Ophthalmol* 1981; 91: 297-311.
- 9 Carney MD, Paylor RR, Cunha-Vaz JG, Jampol LM, Goldberg MF. Iatrogenic choroidal neovascularization in sickle cell retinopathy. *Ophthalmology* 1986; 93: 1163-8.
- 10 Moriarty BJ, Acheson RW, Serjeant GR. Epiretinal membranes in sickle cell disease. *Br J Ophthalmol* 1987; 71: 466-9.
- 11 Moriarty BJ, Acheson RW, Condon PI, Serjeant GR. Patterns of visual loss in untreated sickle cell retinopathy. *Eye* 1988; 2: 330-5.