ARE THERE MEDICAL CONDITIONS SPECIFICALLY UNDERLYING THE DEVELOPMENT OF RUBEOSIS IN CENTRAL RETINAL VEIN OCCLUSION?

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SUMMARY

Two hundred and thirty five patients with central retinal vein occlusion (mean age 64.9 years, 95% CI (63.3, 66.5) years), comprising 221 white Europeans, 10 Asians and 4 West Indians) were studied over a 7 year period of whom 13.2% (n = 31) developed rubeosis (mean age 70.1 years, 95% CI (66.3, 73.9) years; all white Europeans). Comparisons were made with 31 of the original 235 CRVO patients who did not develop rubeosis, and who were individually matched for age, sex and ethnic origin. The 31 patients developing rubeosis were significantly older (p = 0.013) than the 204 patients not developing rubeosis (mean age 64.1 years, 95% CI (62.3, 65.9) years). There was no significant difference between the CRVO group with rubeosis and the uncomplicated matched CRVO group in the prevalence rates of hypertension (64.5% vs. 45.2%), hyperlipidaemia (48.4% vs. 38.7%) or diabetes mellitus (9.7% vs. 12.9%). We conclude that neovascular glaucoma is more likely to occur in older subjects with CRVO.

The major complications of central retinal vein occlusion (CRVO) include neovascularisation and neovascular glaucoma.[1] The development of these complications is considered to be related to ocular ischaemia. Identifying those patients with CRVO who are at high risk of developing neovascular complications is important as effective prophylactic treatment with panretinal photocoagulation is available.[2]

Ophthalmic examination (in particular the number of retinal cotton wool spots and the presence of an afferent pupillary defect),[3,4] fluorescein angiography[5,6] and electrodiagnostic tests[7–9] may be of benefit in helping to predict which eyes with CRVO will proceed to neovascular complications.

Systemic associations of CRVO are well described and include hyperlipidaemia, hypertension, diabetes mellitus, hyperproteinaemia and polycythaemia.[10–14] The development of rubeosis in CRVO has been associated with the presence of systemic hypertension, diabetes mellitus, atherosclerotic cardiovascular disease, ischaemic heart disease, cardiac enlargement, increasing age, and primary open angle glaucoma or ocular hypertension.[15,16]

We reviewed the case notes of all patients attending the Birmingham and Midland Eye Hospital with CRVO in order to determine the presence of any specific underlying medical conditions associated with the development of rubeosis iridis or neovascular glaucoma, and, if possible, to identify a subgroup of CRVO patients at increased risk of developing these neovascular complications.

PATIENTS AND METHODS

All patients with CRVO (n = 235) who attended the medical ophthalmology clinic (E.E.K.) at the Birmingham and Midland Eye Hospital in the 7 year period between 1982 and 1989 have been studied. The diagnosis of CRVO was made clinically, based on the characteristic fundus appearance of a swollen optic disc, engorged retinal veins, and scattered fundus haemorrhages in all quadrants. Ophthalmic examination for all patients included visual acuity assessment, slit lamp examination and applanation tonometry. Gonioscopy was undertaken to detect the presence of rubeosis involving the angle. Fluorescein angiography was not routinely performed. For the purpose of this study, rubeosis was defined as the presence of rubeosis iridis with or without neovascular glaucoma.

All patients were referred to the Physicians Clinic (P.M.D.) whre a full medical history and clinical examination were recorded. Investigations included a full haematological profile, urea and electrolyte levels, liver function tests, immunoglobulin levels, fasting lipids and blood glucose levels, chest radiograph and electrocardiogram. The blood pressure was recorded after 5 minutes of rest in the sitting and supine positions on an Accuson sphygmomanometer and the mean recorded. The diastolic

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Table I. Comparison of the 31 CRVO patients developing rubeosis with the 204 patients not developing rubeosis

	Did not develop rubeosis (n = 204)	Developed rubeosis (n = 31)
Age (yr)		
Mean	64.1	70.1*
SD	12.8	10.5
Sex		
Male	103 (50.5%)	13 (41.9%)**
Female	101 (49.5%)	18 (58.1%)
Ethnic origin		
Caucasian	190 (93.1%)	31 (100%)
Asian	10 (4.9%)	0
West Indian	4 (2.0%)	0

*p = 0.013; **p = 0.487.

pressure was recorded at the fifth Korotkoff phase. The appropriate cuff correction for obesity was made.

Hypertensive patients were defined, according to World Health Organisation criteria, as those with a systolic pressure of greater than 160 mmHg or a diastolic pressure greater than 95 mmHg on three occasions, or those on established antihypertensive drug therapy. Hyperlipidaemia was defined as a fasting serum cholesterol of greater than 6.5 mmol/l or a fasting serum triglyceride of greater than 2.1 mmol/l. Serum cholesterol and triglycerides were measured by standard semi-automated techniques. The electrocardiograms were coded according to a modified Minnesota code.

The patients who developed rubeosis over the 7 year period were individually matched by age (to within 4 years), sex and ethnic origin to patients with CRVO not developing rubeosis. Statistical comparisons for unmatched data were performed using the chi-squared test for prevalence rates and the unpaired t-test for continuous variables. The matched data were analysed using McNemar's test for categorical variables and the paired t-test or the Mann–Whitney test (on the paired differences) for continuous variables.

Table II. Clinical details of 31 patients with CRVO and rubeosis, and a matched group of 31 CRVO patients without rubeosis

	CRVO with rubeosis (n = 31)	CRVO without rubeosis (n = 31)
Age		
Mean	70.1	70.4*
SD	10.5	10.3
Sex		
Male	13	13 (41.9%)
Female	18	18 (58.1%)
Ethnic origin		
Caucasian	31	31 (100%)
Weight (kg)		
Median	63.5	67.1
IQR	(52.5, 77.5)	(59.4, 80.0)
n	13	19
Smoker		
Current	9	9**
Ex	5	1
Non	17	21
Alcohol[a]		
>1 unit/day	5	2
>4 units/day	0	0
None or <1 unit/day	23	29

IQR, inter-quartile range (25th percentile, 75th percentile).
*p = 0.34; **p = 0.42.
[a]1 unit of alcohol = 7.5 g.

RESULTS

Thirty-one (13.2%) of the 235 patients with CRVO developed rubeosis (Table I). This group was significantly older than the group not developing rubeosis [p = 0.013, mean difference 6 years, 95% CI (confidence interval) (1.3, 10.8) years], contained a higher percentage of females, and consisted of Caucasian only. One patient had bilateral CRVO with rubeosis.

The 31 patients developing rubeosis were compared with 31 of the original 235 patients with CRVO who did not develop rubeosis, and were individually matched for age, sex and ethnic origin (Table II). The prevalence rates of underlying medical conditions (Table III) and the median biochemical values (Table IV) in the two groups were compared. The 32 eyes with rubeosis comprised 5 eyes with rubeosis iridis (15.6%) and 27 eyes with neovascular glaucoma (84,4%).

There were no significant differences between the matched groups with respect to age (p = 0.34) or the proportion of current or ex-smokers (p = 0.42). Weight and

Table III. Prevalence rates of underlying medical conditions in 31 CRVO patients with or without rubeosis

	CRVO with rubeosis (n = 31)	CRVO without rubeosis (n = 31)
Hypertension		
New case	13	4*
Established	7	10
n	31	31
Hyperlipidaemia		
Hypercholesterolaemia	10	8**
Hypertriglyceridaemia	1	1
Combined	4	3
n	31	31
Diabetes mellitus		
Established	2	3
New	1	1
n	31	31
Hyperfibrinogenaemia		
Yes	10	7
No	13	18
Renal failure		
Yes	3	2
No	28	29
Hyperimmunoglobulinaemia		
Yes	4	2
No	10	2
Angina		
Yes	3	1
No	28	30
Cerebrovascular accident		
Yes	2	1
No	29	30
Myocardial infarction		
Yes	0	1
No	31	30

*p = 0.21; **p = 0.61.

Table IV. Median biochemical values in 31 CRVO patients with or without rubeosis

	CRVO with rubeosis (n = 31)	CRVO without rubeosis (n = 31)	p value
Cholesterol (mmol/l)			
n	31	31	0.47
Median	6.5	6.2	
IQR	(5.0, 7.5)	(5.4, 7.0)	
Triglyceride (mmol/l)			
n	30	31	0.57
Median	1.4	1.3	
IQR	(1.0, 2.0)	(0.9, 1.8)	
Fasting blood sugar (mmol/l)			
n	31	30	0.36
Median	4.9	4.9	
IQR	(4.5, 5.4)	(4.5, 5.4)	
ESR (mm/1st hour)			
n	30	25	0.54
Median	11.0	10.0	
IQR	(5.0, 23.5)	(3.5, 20.0)	
Fibrinogen (g/l)			
n	22	25	0.81
Median	4.1	4.0	
IQR	(3.4, 4.9)	(3.3, 4.4)	
Gamma globulins (IU/l)			
n	19	21	0.75
Median	23.0	23.0	
IQR	(17.0, 47.0)	(18.0, 33.5)	
Creatinine (μmol/l)			
n	8	3	
Median	110.5	121.0	
IQR	(101.2, 208.3)	(108.0, 133.0)	

IQR, inter-quartile range (25th percentile, 75th percentile); ESR, erythrocyte sedimentation rate.

the proportion of alcohol drinkers (>1 unit/day) appeared similar in the two groups although the numbers of both were too small to be tested for statistical significance.

The prevalence of hypertension, particularly newly diagnosed hypertension, and of hyperlipidaemia were increased in the group developing rubeosis. Calculation of the relative risks showed an increased risk of developing rubeosis in patients with hypertension [relative risk 2.2, 95% CI (0.7, 6.5)] and hyperlipidaemia [relative risk 1.5, 95% CI (0.5, 4.3)], although these were not found to be statistically significant (p = 0.21 and p = 0.61 respectively). The prevalence rates of the other medical conditions were too low to be tested for statistical significance.

The patients with raised immunoglobulin levels in the rubeotic group comprised 2 patients with an elevated IgA (both 4.4 g/l; normal range 0.8–4.0 g/l), 1 patient with an elevated IgG (17.5 g/l; normal range 5.0–14.0 g/l), and 1 patient with a combined elevation of IgA (4.4 g/l) and IgM (2.5 g/l; normal range 0.5–1.9 g/l). This last patient had an abnormal immunoglobulin band (lambda), but none of the patients had myeloma.

The Mann–Whitney test was used (on the matched differences) to compare the median biochemical values in the two groups, as the data were not normally distributed and the numbers of matched pairs were, in some cases, small. No significant differences between the matched groups were found. Creatinine levels could not be compared due to incomplete data.

Medical conditions which were present in the group developing rubeosis are detailed in Table V. Systemic steroids were being used on a long-term basis by 2 patients, 1 with chronic obstructive airways disease and the other with rheumatoid arthritis. One patient with Eisenmenger's complex had bilateral CRVO with rubeosis. Three patients with mitral valve disease were identified in the rubeotic group, 1 of whom was taking warfarin.

The chest radiograph showed cardiomegaly in 13 patients (41.9%), and the electrocardiogram showed ischaemia in 9 patients (29.0%) in the rubeotic group. Primary open angle glaucoma was present in 3 (9.7%) and ocular hypertension in 2 (6.5%) of the 31 patients developing rubeosis.

DISCUSSION

Many previous studies on the investigation of the systemic associations of retinal vein occlusion combined branch and central retinal vein occlusions, which may have different aetiological factors. The neovascular complications in the two groups also differ, with branch retinal vein occlusions more likely to develop new vessels on the disc or elsewhere and CRVO patients more likely to develop rubeosis iridis or neovascular glaucoma.[1] Investigations of CRVO patients developing rubeosis have also produced conflicting results.[1,15] Our study considers only CRVO patients, and compares a group developing rubeosis with a carefully matched group with CRVO who did not develop this complication.

The results suggest that increasing age is associated with the development of rubeosis in CRVO. There was no significant difference between the CRVO group with rubeosis and the uncomplicated matched CRVO group in the prevalence rates of hypertension, hyperlipidaemia, diabetes mellitus, median ESR and serum fibrinogen, smoking habits and level of alcohol consumption, indicating that these are not useful predictive factors for the development of rubeosis in CRVO. Primary open angle glaucoma or ocular hypertension was present in five patients (16.1%) developing rubeosis, and this association has previously been recognised.[15] There were no cases of rubeosis in the non-Caucasian patients presenting with CRVO, which may be a further manifestation of ethnic differences in this condition.[17]

One of the main problems in CRVO is predicting which eyes are most likely to develop rubeotic complications. We were unable to demonstrate any specific underlying medical conditions associated with a significant increased risk of developing rubeosis in CRVO. However, special

Table V. Medical conditions present in the 31 CRVO patients with rubeosis

Medical diagnosis	No. of patients
Chronic obstructive airways disease	4
Valvar heart disease	3
Eisenmenger's complex	1
Rheumatoid arthritis	1
Hypothyroidism	1

attention should be paid to older subjects presenting with this condition.

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Key words: Central retinal vein occlusion, Hyperlipidaemia, Hypertension, Neovascular glaucoma, Rubeosis iridis.

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