

Medical conditions underlying retinal vein occlusion in patients with glaucoma or ocular hypertension

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SUMMARY Forty-three patients with glaucoma and 24 patients with ocular hypertension presenting with a retinal vein occlusion were medically assessed. The prevalence of systemic hypertension was 60.5% in those with glaucoma and 66.6% with ocular hypertension. The prevalence of hyperlipidaemia was 38.1% in those with glaucoma and 37.5% in those with ocular hypertension. These findings were compared with those from a carefully age-sex matched group of patients presenting with a retinal vein occlusion without evidence of glaucoma or ocular hypertension. There were no statistical differences between any of the groups (52.2% had systemic hypertension and 28.8% had hyperlipidaemia). There was also a strikingly high prevalence of systemic hypertension (89%) and hyperlipidaemia (55.5%) in nine of the patients who had evidence of a recurrent retinal vein occlusion associated with glaucoma, and these prevalence rates were strikingly similar to the rates in patients with recurrence but without glaucoma. The data suggest that glaucoma or ocular hypertension has a less prominent aetiological role in the development of a retinal vein occlusion than underlying medical causes and that full medical assessment is worthwhile.

An association between central retinal vein occlusion and chronic simple glaucoma has been recognised for many years.¹⁻⁴ Similarly, central retinal vein occlusions occur in 3% of patients with ocular hypertension.⁷ The association between branch retinal vein occlusion and glaucoma is less clear.¹⁻⁶ However, hemisphere vein occlusion with the obstruction occurring at the edge of the optic cup is considered to be unquestionably related.⁸ From another point of view retinal vein occlusion has well established associated medical conditions, and a comparison between the prevalence in patients with retinal vein occlusion preceded by glaucoma or ocular hypertension, and patients with retinal vein occlusion without evidence of glaucoma or ocular hypertension, may give a hint to the importance of glaucoma or ocular hypertension in the aetiology of retinal vein occlusion.

We therefore performed a study to ascertain the prevalence of associated medical conditions in a group of patients with the combination of retinal vein occlusion and preceding glaucoma or ocular hyper-

tension and compared them with a group of patients presenting with retinal vein occlusion without evidence of glaucoma or ocular hypertension who had been matched for age, sex, and vein occlusion type. The aetiological role of glaucoma or ocular hypertension in retinal vein occlusion and the value of medically investigating these patients is thus considered.

Patients and methods

Sixty-seven patients with retinal vein occlusion together with either glaucoma or ocular hypertension were assessed and divided into two groups. The first group included 43 patients with glaucoma who subsequently presented with a retinal vein occlusion. The second group included 24 patients with ocular hypertension who likewise presented with a retinal vein occlusion. The clinical details are presented in Table 1. Patients were excluded if rubeosis was present at the time of the diagnosis of glaucoma or ocular hypertension.

We defined ocular hypertension as an intraocular pressure (IOP) of greater than 21 mm Hg⁹ in either

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Table 1 Clinical details of the patients with retinal vein occlusion both with and without ocular hypertension or glaucoma

| | Glaucoma patients | Isolated RVO comparison | OHT patients | Isolated RVO comparison |
|-------------|-----------------------|-------------------------|-----------------------|-------------------------|
| Number | 43 | 43 | 24 | 24 |
| Sex | 25M:18F (1:39:1) | 25M:18F (1:39:1) | 11M:13F (0:85:1) | 11M:13F (0:85:1) |
| Mean age | 68.47 (SD 9.6) | 68.79 (SD 9.3) | 68.75 (SD 8.5) | 69.42 (SD 8.2) |
| Mean weight | 74.41 Kg (SD 11.8) | 72.54 Kg (SD 14.0) | 71.92 Kg (SD 15.1) | 67.28 Kg (SD 14.4) |
| RVO type | 32 CRVO 11 BVO | 32 CRVO 11 BVO | 15 CRVO 9 BVO | 15 CRVO 9 BVO |

RVO=retinal vein occlusion. OHT=ocular hypertension. No statistical differences between the groups were found.

eye, noting that, once a vein occlusion had occurred, the IOP in that eye may fall for up to two years.¹⁰ Where possible more than one recording was used to confirm raised IOP; however, most patients had been diagnosed before attending the clinic.

Glaucoma was defined as occurring in an eye with abnormally raised IOP in which there was pathological cupping of the optic disc with corresponding visual field defects. The optic disc may be swollen in retinal vein occlusion and thus may mask the presence and extent of cupping. Likewise there may be visual field defects which could equally be caused by glaucoma or retinal vein occlusion. Allowance therefore had to be made for these diagnostic problems. There were 37 patients with open angle glaucoma, two with chronic angle closure glaucoma, and one with glaucoma secondary to a blunt injury. We also included one patient who had acute angle closure glaucoma and central retinal vein occlusion concurrently despite the fact that the resulting visual field and optic disc appearance was normal, and two patients with low tension glaucoma.

Retinal vein occlusion was diagnosed on clinical grounds. In view of the significant number of patients with glaucoma who develop retinal vein occlusion silently¹¹ we assumed newly discovered shunt vessels on the disc in the absence of orbital disease to indicate the presence of a central retinal vein occlusion. The diagnosis was confirmed by slit-lamp examination, gonioscopy, direct and indirect ophthalmoscopy, and visual field assessment. Retinal vein occlusion was subdivided into a central form, including six patients with shunt vessels on the optic disc, and that of a branch occlusion, which included five patients with hemisphere vein occlusion.

The patients were then examined by a physician, and the following laboratory investigations were

Table 2 Prevalence of medical conditions underlying retinal vein occlusion with and without glaucoma or ocular hypertension

| | Hypertension | Hyperlipidaemia | Diabetes |
|-------------------------|--------------------|--------------------|-------------------|
| Glaucoma patients | 26 (60.5%) n=43 | 16 (38.1%) n=42 | 2 (4.9%) n=41 |
| OHT patients | 16 (66.6%) n=24 | 9 (37.5%) n=24 | 5 (20.8%) n=24 |
| Isolated RVO comparison | 35 (52.2%) n=67 | 19 (28.8%) n=66 | 5 (7.5%) n=67 |

OHT=ocular hypertension. RVO=retinal vein occlusion. For ease of presentation in Tables 2, 3, and 7 the values were used for all the patients with RVO together as a comparison group. No statistical differences were observed between the groups.

carried out for each patient: full haematological profile, blood urea, electrolytes, liver function tests, protein electrophoresis and immunoglobulin levels, fasting lipid profile, blood glucose, chest x-ray, and electrocardiogram (ECG).

The blood pressure was recorded after five minutes' rest in the sitting and supine positions on an Accuson sphygmomanometer and the mean recorded. The diastolic pressure was recorded at the fifth Korotkoff phase.

Hypertension was defined according to the World Health Organisation criteria as a systolic pressure of greater than 160 mm Hg and a diastolic pressure of greater than 95 mm Hg on three occasions, or when a patient was already established on antihypertensive drug therapy. Hyperlipidaemia was defined as a fasting serum cholesterol level of greater than 7.1 mmol/l or a fasting serum triglyceride level of greater than 2.1 mmol/l. Serum cholesterol and triglyceride were measured by standard semi-automated techniques.

The comparison groups were taken from patients attending the same hospital with a retinal vein occlusion alone without evidence of glaucoma or ocular hypertension. They were closely matched for age, sex, and type of vein occlusion, and their clinical details are presented in Table 1. Statistical comparisons were made by the unpaired *t* test, and the χ^2 test.

Results

Tables 2 and 3 show the prevalence and mean values of associated medical diseases in the groups.

No statistical differences were observed in the prevalence of hypertension and hyperlipidaemia between the glaucoma or ocular hypertension groups and the matched groups, and the prevalence rates were also comparable in the glaucoma and the ocular hypertension groups. Diabetes mellitus was relatively uncommon in all three groups.

Table 3 Mean values of systemic and diastolic blood pressure, cholesterol, and triglyceride levels in the major groups

| | Mean systolic BP (mm Hg) | Mean diastolic BP (mm Hg) | Mean serum cholesterol (mmol/l) | Mean serum triglyceride (mmol/l) |
|----------------------|--------------------------|---------------------------|---------------------------------|----------------------------------|
| RVO+glaucoma n=43 | 166.74 (SD 28.1) | 90.26 (SD 10.9) | 6.47 (SD 1.3) | 1.61 (SD 0.8) |
| RVO+OHT n=24 | 166.88 (SD 22.1) | 9.17 (SD 7.0) | 6.51 (SD 1.4) | 1.60 (SD 0.8) |
| RVO control n=67 | 169.33 (SD 29.3) | 90.76 (SD 13.6) | 5.83 (SD 1.6) | 1.38 (SD 0.6) |

RVO=retinal vein occlusion. OHT=ocular hypertension.

Combining the glaucoma and ocular hypertension groups, we found a high prevalence of abnormally raised fibrinogen (mean 4.33 (SD 1.0) g/l, n=61; 37.7% >4.3 g/l), and immunoglobulin levels, especially IgA (mean 2.96 (SD 1.2) g/l, n=44; 25% >4.0 g/l). Only 24 patients had their plasma viscosity estimated, but 20 of these had levels of 1.8 cp or more. There were nine patients with raised haemoglobin levels (>16 g/dl), but none had a packed cell volume of greater than 50%. The mean erythrocyte sedimentation rates (ESR) were not significantly raised. Other important medical conditions were also identified in the two groups, and are presented in Table 4.

Nine patients (13.4%) were recorded to be active smokers and 11 (16.4%) past smokers. Four had a moderate alcohol intake; one had a past history of high alcohol consumption.

Nine patients (13.4%) had evidence of a previous retinal vein occlusion in the other eye (that is, recurrent retinal vein occlusion). The prevalence of hypertension and hyperlipidaemia in this group was strikingly high (Table 5). Data are also included showing the prevalence rates in a previous study from the same hospital by Dodson *et al.*¹² of 17 patients with recurrent retinal vein occlusion without evidence of glaucoma or ocular hypertension, and a striking similarity is apparent.

There were 11 patients (16.4%) in the glaucoma

Table 4 Other associated medical conditions in patients with ocular hypertension or glaucoma

| Medical condition | Number |
|-----------------------------|--------|
| Aortic/mitral valve disease | 4 |
| Chronic renal failure | 3 |
| Carcinoma (1 on tamoxifen) | 3 |
| Chronic lymphatic leukaemia | 1 |
| Myeloma | 1 |
| Giant cell arteritis | 1 |

Table 5 Patients with recurrent RVO

| | Recurrent RVO with glaucoma or OHT (Present study) | Recurrent RVO without glaucoma or OHT (Dodson <i>et al.</i> ¹²) |
|-----------------------|--|---|
| Number | 9 | 17 |
| Sex | 7M:2F | 9M:8F |
| Mean age | 60.66 | 65.94 |
| Hypertension | 8 (89%) | 15 (88%) |
| Hyperlipidaemia | 5 (55.5%) | 8 (47%) |
| Hypercholesterolaemia | 4 (44.4%) | 6 (35%) |
| Hypertriglyceridaemia | 3 (33.3%) | 4 (24%) |

RVO=retinal vein occlusion. OHT=ocular hypertension.

and ocular hypertension groups combined who had no associated medical conditions. Their mean IOP at the time of diagnosis was compared with that of the remaining patients, apart from those with neovascular glaucoma (Table 5). There was no statistical difference between the mean levels in the two groups. They were higher than 21 mm Hg in the affected eye in both groups (Table 6). A similar result was also seen in the unaffected eye apart from eyes with rubeosis.

The prevalence of associated medical conditions in patients with a central retinal vein occlusion were also analysed separately and compared with the prevalence rates in patients with the branch form. The results are presented in Table 7, and shows a trend towards a slightly higher prevalence of both hypertension and hyperlipidaemia in patients with the branch form, especially hypertension in the ocular hypertensive group.

Shunt vessels on the optic disc may not be conclusive evidence of central retinal vein occlusion. However, removing from the analysis the six patients whose central retinal vein occlusion was diagnosed on the presence of collaterals on the optic disc makes no difference to the results.

Discussion

The relationship between glaucoma and central retinal vein occlusion was first recognised in 1913 by

Table 6 Comparison between the mean intraocular pressures recorded in a group of patients who had no associated medical conditions and in the remaining patients apart from those with rubeosis

| | No associated medical condition | Remainder |
|-------------------------------|---------------------------------|------------|
| Mean IOP affected eye (mm Hg) | 24.36 n=11 | 24.24 n=54 |
| Mean IOP other eye (mm Hg) | 24.45 n=10 | 23.33 n=49 |

Table 7 Prevalence of hypertension and hyperlipidaemia in patients with glaucoma or ocular hypertension with CRVO compared with patients with branch RVO and an isolated RVO comparison group

| Hypertension | | | | |
|-----------------|--------------------|-------------------|--------------------|-------------------------|
| | Glaucoma | OHT | Total | Isolated RVO comparison |
| CRVO | 20 (62.5%) n=32 | 8 (53.3%) n=15 | 28 (59.6%) n=47 | 29 (61.7%) n=47 |
| BVO | 6 (54.5%) n=11 | 8 (88.8%) n=9 | 14 (70%) n=20 | 8 (40%) n=20 |
| Hyperlipidaemia | | | | |
| | Glaucoma | OHT | Total | Control |
| CRVO | 11 (35.5%) n=31 | 5 (33.3%) n=15 | 16 (34.8%) n=46 | 12 (28.8%) n=46 |
| BVO | 5 (45.5%) n=11 | 4 (44.4%) n=9 | 9 (45%) n=20 | 7 (35%) n=20 |

RVO=retinal vein occlusion. CRVO and BVO=central retinal vein occlusion and branch vein occlusion respectively. OHT=ocular hypertension.

Verhoeff.¹³ Subsequently several authors have reported on the high incidence of retinal vein occlusion in patients with glaucoma. Primary open angle glaucoma is a feature which precedes central retinal vein occlusion, with a prevalence ranging from 5.7% to 65.5%. Most studies show a prevalence between 10 and 40%.¹⁻⁶ In contrast, the prevalence of primary open angle glaucoma in branch vein occlusion appears to be less frequent at between 6.6% and 15%.^{1-4,6}

Prospective studies have also suggested a link. For example, Dobree found that 4.5% of patients with chronic open angle and closed angle glaucoma, after one to eight years' follow-up, developed a retinal vein occlusion.¹⁴ David *et al.* found a similar rate of 3% in patients with ocular hypertension after one to 11 years.⁷

The explanation for the association between glaucoma and retinal vein occlusion has yet to be elucidated. Some authors have considered that these conditions are not related aetiologically but rather are both manifestations of some underlying vascular abnormality.^{4,15} Systemic hypertension is not related to chronic simple glaucoma; in fact the mean systolic blood pressure in patients with glaucoma has been shown to be low.¹⁶ There are conflicting reports of the incidence of hyperlipidaemia in patients with glaucoma or ocular hypertension,^{17,18} though risk factors in low tension glaucoma include hypertension, diabetes mellitus, hyperlipidaemia, and raised blood and plasma viscosities.¹⁹ A similar IOP response to postural changes in eyes with chronic

glaucoma and eyes following vein occlusion was suggested by Williams and Peart to be indicative of an underlying vascular abnormality.²⁰ This may be particularly relevant in the case of retinal vein occlusion not related to raised IOP, as it is well documented that the primary event is endothelial cell proliferation in the vein wall associated either with degeneration of the endothelium and secondary thrombus formation or with severe phlebosclerosis.²¹ The exact mechanism underlying the primary event is not clear, but clinical studies indicate that it is multifactorial, with cardiovascular risk factors such as hypertension and hyperlipidaemia prominent.^{12,22-24} Other abnormalities have been identified and include abnormal in-vivo platelet function,^{25,26} hyper-viscosity,²⁷ and perhaps increased inflammatory activity.²⁷⁻²⁹

The results in this study do, however, demonstrate that the prevalence of associated medical conditions in patients with retinal vein occlusion either with or without glaucoma or ocular hypertension are markedly similar. This observation holds for hypertension, hyperlipidaemia, diabetes mellitus, and smoking habits. The other abnormalities found with raised fibrinogen, IgA, and plasma viscosity levels are also consistent. The striking resemblance between those patients with recurrent retinal vein occlusion with preceding glaucoma or ocular hypertension and a previously reported group from the same hospital with recurrent retinal vein occlusion alone would also strongly support the similarity between the two groups.¹² These findings imply that glaucoma or ocular hypertension may not be the most important aetiological factor and that the associated medical conditions may be of greater significance.

The relationship between IOP, retinal blood flow, and systemic arterial pressure is complex. Under normal circumstances the ocular blood flow is chiefly determined by the level of the systemic arterial and intraocular pressures, the blood viscosity, and the state of the blood vessels supplying the eyes.³⁰ In response to raised IOP autoregulation occurs, with an increase of pressure in the arteries outside the eye and decreased vascular resistance in the retina to maintain normal blood flow.³¹

It may be that for these patients with a compromised circulation, and possibly compromised autoregulatory mechanisms, a minor rise in IOP is high enough to reduce ocular blood flow sufficiently to propagate stagnant blood flow. This hypothesis is supported by the finding of a reduction in IOP thresholds, normally estimated to be 27-30 mm Hg in patients with chronic simple glaucoma, up to which autoregulation, by increasing arterial pressure with decreased vascular resistance, maintains normal blood flow.³²

Although we do not know the exact IOP at the time of a retinal vein occlusion, available evidence would suggest that the pressure may be raised³³ and that the venous occlusive episode itself subsequently has a lowering effect.¹⁰ Only two patients suffered from low tension glaucoma. However, this may simply reflect the incidence of diagnosed low tension glaucoma in comparison with chronic simple glaucoma. Therefore a minor elevation of pressure with a reduction in retinal blood flow might also contribute to a venous occlusion.

Mechanical compression at the site of the venous occlusion is thought by some to compromise the circulation further.³⁴ In patients with central retinal vein occlusion backward bowing of the lamina cribrosa³⁵ or loss of glial support in a pathologically cupped optic nerve head,¹⁴ is thought to be responsible. It has been found, however, that retinal vascular events tend to occur early in the course of the associated glaucoma and not, as might be expected, to be related to the degree of cupping.^{2,35} This again emphasises the more important aetiological role of other factors. Furthermore, no differences between the mean IOPs of patients who had no associated medical condition were found in comparison with the remainder, which implies that even in this group the raised IOPs might still have only a minor role.

Management of a patient with a retinal vein occlusion with or without glaucoma or ocular hypertension should include the identification and treatment of common conditions which appear to have an aetiological role in retinal vein occlusion. Other serious medical disorders, including carcinoma of breast, myeloma, and chronic lymphatic leukaemia, were identified in our group, and emphasise the importance of medical investigation.

Retinal vein occlusion appears to be linked with an increase in vascular causes of death (cardiac and cerebral),³⁶ and there is evidence that treatment of hypertension and hyperlipidaemia can reduce the severity of some of its complications. Identification of these factors should therefore offer an opportunity for effective therapy.³⁷⁻³⁹ Indeed the result in reducing the rate of devastating recurrence of retinal vein occlusion from 10-15%, as previously reported, to 1%, as suggested in a preliminary study after a five-years follow-up,²² is encouraging.

However tenuous the evidence may be, control of the IOP on theoretical grounds should still be considered important. It may also be important to establish the effect of drugs on the capacity of the autoregulatory mechanisms in the retina. Grunwald found that timolol enhances autoregulation of retinal blood flow, and suggested that this may help perfusion following retinal vein occlusions.⁴⁰ Other antiglaucoma drugs may affect this capacity. The

treatment given for controlling systemic hypertension may also affect the control of the IOP, and perhaps autoregulation. These factors need further investigation.

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