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Chronic open-angle glaucoma and ocular hypertension
An epidemiological study

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Vascular conditions have recently received considerable attention in studies of chronic open-angle glaucoma (Begg, Drance, and Sweeney, 1971; Morgan, 1972; Drance, Morgan, and Sweeney, 1973a; Drance, Sweeney, Morgan, and Feldman, 1973b; Schwartz, 1973) These conditions include blood pressure, hypotensive crises, and the vascular changes of diabetes (Becker, 1971). The nerve fibre bundle defects produced by hypotensive crises are indistinguishable from those due to glaucoma; the results of these hypotensive crises seem to be most important in persons with normal ocular tension. (Drance and others, 1973a).

As part of a larger epidemiological study, a number of variables related to vascular disease were included to identify the possible relationships of these variables to the presence or absence of chronic open-angle glaucoma. From current knowledge of the epidemiology of atherosclerotic vascular disease, we developed a number of hypotheses, all based on the assumption that systemic or arterial factors which might lead to diminished perfusion at the optic nerve head would predispose to glaucomatous change. The hypotheses were as follows:

H_1 Glaucoma patients would have a greater frequency of previous coronary artery disease, cerebrovascular disease, or peripheral vascular disease than a matched control group.

H_2 Glaucoma patients would have a stronger family history of coronary artery disease or cerebrovascular disease than controls.

H_3 Glaucoma patients would have a worse smoking history than controls.

H_4 Glaucoma patients would have a greater frequency of previous haemodynamic crises than controls.

H_5 Glaucoma patients would have a higher frequency of diabetes mellitus than controls.

Because of an opportunity to study, in the same fashion, ocular hypertensives as well as glaucoma patients, the current study also examines a similar set of hypotheses as they relate to ocular hypertension with no evidence of visual defect or change in disc appearance.

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Methods

All practising ophthalmologists in the Province of British Columbia were asked to report, for a period of one year, all *new* cases of glaucoma on a standardized report form. These cards were sent to a Central Registry initiated and maintained by the British Columbia Division of the Canadian National Institute for the Blind. The cases collected in this fashion were supplemented by a large number of previously diagnosed cases drawn from the Department of Ophthalmology of the University of British Columbia, and from a private practitioner with a large glaucoma referral practice.

All patients were interviewed in their homes by the same experienced interviewer. At the completion of the interview, she selected the house fourth away on the right-hand side. At that house, she sought a control of same age (±5 years) and sex as the patient. If she was unsuccessful, she continued to the next house, and so on. Few eligible respondents refused. Cases and controls were totally matched for sex and practically identical in education and income levels. Data concerning matching are available on request.

Interviews were highly structured and each lasted 15 to 45 minutes, depending on the health history, family size, etc.*

An experienced ophthalmologist (SMD) reviewed all cases reported to the Registry and placed them into one of the following categories:

(A) Chronic open-angle glaucoma (ocular tension > 21 mm. Hg. with optic disc change and field defect).

(B) Ocular hypertension (tension over 21 mm. Hg).

(C) Low tension glaucoma.

(D) Other.

For this study, only persons in Categories A and B were included.

* A sample questionnaire is available on request.

Results

Reporting by most of the ophthalmologists in private practice was less than expected. Originally, it was hoped to estimate annual incidence in the population: the data are not sufficient for this purpose. Because many of the ophthalmologists did not report any cases, the patients in the current study cannot be considered entirely representative of the population. This is no way invalidates the hypothesis testing, but precludes generalization to the whole population.

Data are presented here in the form of case-control pairs, rather than by individuals. This is appropriate for a study with matched pairs and allows the use of the McNemar χ^2, a test more appropriate than the more commonly used χ^2. Table I demonstrates the display of data. If both persons in the pair have the characteristic under study (*e.g.* diabetes), the pair is counted (one only) in cell *p*. Conversely, if neither member is diabetic, the pair appears in cell *s*.

For some variables, Tables also include measures of relative risk, usually computed by the formula *q*/*r*, using the notation in Table I. This is an expression referring to the risk of disease, given the presence of the variable under study. This risk is expressed relative to those persons not possessing the particular variable. That is to say, if smokers had a relative risk of 2·0, smokers would be twice as likely as non-smokers to have the disease under study.

Data are analysed separately for glaucoma patients and ocular hypertensives.

(*A*) *Glaucoma patients* (Table II)

The excess of cases over controls who had previously received blood transfusions suggests that a history of previous transfusion is related to current chronic simple glaucoma. The relative risk of 3·0 suggests that people of this age, with a history of receiving blood transfusions, have triple the risk of having glaucoma. Our data fail to implicate diabetes as a major factor in the aetiology of glaucoma. While the prevalence in cases exceeds the level in controls, diabetes is still relatively uncommon in both groups. Thus, while a diabetic may be at high risk of the disease, relatively few glaucoma patients have diabetes. Cases had an excess of migraine compared to controls; while this difference did not achieve statistical significance, numbers are rather small adequately to examine the relationship.

Case and control experience for hypertensive therapy appears similar; there is no evidence, that lowering of blood pressure is associated with glaucoma with raised pressure. Although no Tables are included here, cases and controls also showed

Table I *Explanation of calculations*

		Control	
		+	−
Patient	+	*p*	*q*
	−	*r*	*s*

$$\chi^2 = \frac{(|q-r|-1)^2}{q+r} \qquad \text{Relative risk} = \frac{q}{r}$$

\+ indicates presence of variable
− indicates absence of variable

Table II *Risk factors for glaucoma among 91 pairs of patients and controls*

Factor	*Percentage positive*		*No. of informative pairs*	*Relative risk*	χ^2	*Significance* (*P value*)
	Cases	*Controls*				
Previous transfusion	13·2	4·4	16	3·0	3·06	<0·1
Diabetes	6·6	2·2	8	3·0	1·12	NS
Migraine	12·1	5·5	14	2·5	1·79	NS
Treatment for systemic hypertension	18·7	20·9	26	1·0	0·04	NS
Smoking (>20 cig./day)	11·0	13·2	20	1·0	0·05	NS
Paternal eye history	14·3	8·8	17	2·0	0·94	NS
Maternal eye history	22·0	7·6	17	7·5	8·47	<0·005
Outdoor work environment	15·4	28·5	28	0·4	4·32	<0·05

similar rates of stroke, heart disease, and peripheral vascular disease. It thus appears that systemic vascular disease or its treatment has no clear association with this type of glaucoma.

Table II also displays data concerning cigarette smoking. This is but one of many analyses examining the relationship of amount and duration of smoking and case-control status. Analysis demonstrated no association between smoking and disease; smoking histories of cases and controls were virtually identical. The effect of smoking on the vascular component of chronic simple glaucoma appears minimal, if present at all.

We collected data concerning parental history of serious eye problems. It is normally expected that patients will report more parental disease than controls, even when a disease has no familial tendency. This is because patients are more likely than controls to have enquired about a family history of eye disease. It is difficult to explain an excess of maternal eye disease over paternal disease, especially since glaucoma does not affect women more than men. Neither should the increased life expectancy of women produce so much more disease than in men.

It has been speculated that chronic outdoor exposure may predispose to glaucoma (Björnsson, 1967). Our results show a significant amount of *protection* (relative risk = 0·4) bestowed by a work pattern primarily outdoors. Since the cases and controls are matched for age, sex, marital status, and socioeconomic status, there is no obvious demographic explanation for the differences in work pattern. Thus, indoor workers appear to have 2·5 times more risk of glaucoma than outdoor workers.

Glaucoma patients did not differ from controls in patterns of parental mortality, especially as regards age at death or death from vascular causes. This lessens the likelihood that these glaucomatous patients had their condition as a result of an inherited tendency to systemic vascular disease.

(*B*) *Ocular hypertensives* (*without disc and field change*) (Table III)

Unlike the glaucoma patients, ocular hypertensives did not exceed controls in having histories of blood transfusions. Neither did they admit to migraine more frequently than controls.

Diabetes is less frequent in ocular hypertensives than in the controls: this is significant at the 0·01 level. This is the reverse of the glaucoma patients in whom there was a slight (non-significant) increase in the prevalence of diabetes in cases over controls.

Our interviewer asked, "Have you ever been treated for high blood pressure?" The clear excess of controls giving a positive response indicates that ocular hypertensives are less likely than the normal population to have had treatment for raised systemic pressure (relative risk = 0·2; $P < 0·05$).

Like the glaucoma patients, ocular hypertensives did not exceed controls in prevalence of cardiac, peripheral vascular, or cerebrovascular disease, considered separately or together.

All analyses of smoking showed the same thing: ocular hypertensives smoke more heavily than do controls, and are also more likely to be long-time smokers.

Ocular hypertensives had a very slight increase (not significant) in frequency of positive family history for "serious eye problems" over that of the controls. This applied to both maternal and paternal ocular problems.

Unlike the glaucoma patients, the ocular hypertensives did not appear to have an outdoor work experience different from their controls.

Discussion

Since the age and sex distribution of glaucoma patients differs markedly from that of the ocular hypertensives, direct comparisons between the two groups are inappropriate. For example, since the ocular hypertensives are younger than the glaucoma subjects (mean ages 40 and 60 years respectively), one would expect to find a higher prevalence of diabetes in glaucoma patients, as compared to ocular hypertensives. This analytical problem can be overcome, however, by looking at the case-control distributions for each group since each case is matched to a control of virtually the same age. Thus, in comparing results from the two portions of the study, reference will be made to the distribution of the variable by matched pairs (cases and controls) in each half, rather than direct comparisons of cases and controls.

A similar situation applies to the sex ratio in the two study portions. Males represent 54 per cent. of the ocular hypertensives and 40 per cent. of glaucoma patients. Once again, since controls are matched

Table III *Ocular hypertension: risk factors*

Factor	*Informative pairs*	*Relative risk*	χ^2	*P*
Diabetes	8	0·14	3·13	$<0·1$
Treated for systemic hypertension	12	0·20	4·08	$<0·05$
Smoking (>20 cig./day)	13	3·33	2·77	$<0·1$

for sex, comparison of case–control relationship between groups is more appropriate than direct comparisons of glaucoma and ocular hypertensive subjects.

The clear difference in blood transfusion histories of glaucoma patients compared to their controls (Table II), and the lack of difference in the ocular hypertensive group suggest that acute hypotensive episodes sufficient to require transfusion may produce the visual defect and/or disc change which differentiates the glaucoma patient from the ocular hypertensive. This association has previously been demonstrated for low-tension glaucoma (Drance and others, 1973a).

The importance of systemic factors is emphasized by Table IV combining data from both glaucoma and ocular hypertension studies. Although diabetes does not achieve significance as a variable in the glaucoma population, the distribution of discrepant case–control pairs is almost the reverse of that found in ocular hypertension, where there is a significant deficit of diabetics among the cases. From Table IV we can postulate that ocular hypertension combined with diabetes mellitus almost invariably leads to field defect and/or disc change.

One must still speculate on the mechanism responsible for the diabetes–glaucoma association. Since the ocular hypertensives have a low frequency of diabetes, there would seem to be no increase in intraocular pressure associated with diabetes. The field defect and/or disc change most likely reflects local tissue anoxia due to diabetic vascular change.

In comparing the history of treatment for systemic hypertension in the two study groups (Tables II, III, V), one notes that ocular hypertensives have a negative history of treatment more often than their controls, while glaucoma patients resemble their controls. The implications of these findings are not clear but the following are presented as possible explanations:

(*a*) Does treatment for systemic hypertension also relieve ocular hypertension, thus keeping a group of former or potential ocular hypertensives from coming into our study, as they are now ocular normotensives?

(*b*) Does treatment for systemic hypertension precipitate field defects in ocular hypertensives, thus bringing them into the study as glaucoma patients?

(*c*) Does the deficit of treated systemic hypertensives represent an excess of untreated persons in the ocular hypertensive group rather than a deficit of true hypertensives?

(*d*) Are combinations of the above possible?

In any case, the relationship of systemic and ocular hypertension and the effect of treatment will require further study, especially since the medical profession and public are currently being exhorted about the importance of early diagnosis and treatment of essential hypertension.

The total lack of relationship of cardiac, peripheral vascular, or cerebrovascular disease indicates that local conditions of the microcirculation in the eye and optic nerve are probably more important than gross vascular problems. This may be yet another instance in which severity of gross vascular disease fails to correlate well with actual tissue damage due to anoxia. As in other body areas, the presence and quality of collateral circulation may be an important determinant.

We are disappointed in the total lack of relationship of smoking to production of glaucoma. While no relationship of smoking with ocular hypertension

Table IV *Analysis of discrepant case–control pairs in glaucoma and ocular hypertension cases and controls: diabetes*

Diagnosis	*Case non-diabetic Control diabetic*	*Case diabetic Control non-diabetic*
Ocular hypertension	7	1
Glaucoma	2	6

$P < 0.05$ (Exact test, 2-tailed)

Table V *Analysis of discrepant case–control pairs in glaucoma and ocular hypertension cases and controls: treatment of systemic hypertension*

Diagnosis	*Case not treated Control treated*	*Case treated Control not treated*
Ocular hypertension	10	2
Glaucoma	14	12

$P > 0.1$ (Exact test, 2-tailed)

was anticipated, it was reasonable to believe that, if glaucoma has a major vascular component, smoking should appear as a potent factor. Instead, Table III demonstrates a significant excess of smoking among ocular hypertensives, while the glaucoma cases resemble their controls. Naturally, there is a possibility that a real excess of smoking exists in the glaucoma group, but has not been found in this study.

Conclusions

We have presented evidence to suggest that:

(*a*) Glaucoma is related to history of acute blood loss, as signified by transfusions;

(*b*) Diabetes mellitus, while not a major factor in most glaucoma cases, may increase the risk of field defect or disc change in a person with ocular hypertension;

(*c*) The relationship of systemic hypertension and its treatment to ocular hypertension and glaucoma requires clarification;

(*d*) Gross cardiovascular problems are not related, in an important fashion, to risk of having glaucoma;

(*e*) Smoking is associated with an increase in ocular tension, but does not seem to produce glaucomatous changes.

Summary

An epidemiological study of patients with chronic simple glaucoma or ocular hypertension suggests that the diagnosis of glaucoma is associated with a positive family history, acute blood loss, and diabetes mellitus. There was no association with other vascular disease or with smoking. Ocular hypertension was related to smoking habits but not to family history. The relationship of these variables to ocular hypertension/glaucoma status is discussed.

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