Blood groups as genetic markers in glaucoma

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SUMMARY A series of 474 mixed cases of glaucoma was assessed to determine whether there were any genetic differences between different types of glaucoma. A careful distinction was made between chronic open angle glaucoma (COAG), acute and chronic angle closure glaucoma, ocular hypertension, low tension glaucoma, patients with large cup disc ratios, and various types of secondary glaucoma including pseudoexfoliation of the lens capsule, uveitic and traumatic glaucoma. Using ABO blood groups, Rhesus groups, ABH secretion or non-secretion, and phenylthiourea tasting we identified certain differences. The differences from normal were significant decrease in Rh-negative patients in chronic closed angle glaucoma ($p < 0.05$), a decrease in ABH secretors in ocular hypertension ($p < 0.01$), and fewer HB secretors in patients with COAG ($p < 0.02$). There was a significant decrease in AH secretors and increase in HB secretors in both pseudoexfoliation with raised intraocular pressure compared with COAG ($p < 0.01$) and in secondary glaucomas as a group compared with COAG ($p < 0.01$). Tasters of phenylthiourea were more common in traumatic and uveitic glaucoma than in normal controls ($p < 0.05$). These results suggest that secondary glaucoma develops in different subjects from COAG, while patients who develop a rise in intraocular pressure proceed to cupping and field loss if they have a certain genetic constitution. The groups of patients are too small for the differences to be of great prognostic value.

It has been suggested that the distribution of a number of genetically determined characters may act as markers for glaucoma,¹ particularly open angle glaucoma, which occurs more frequently in families² and which is thought to be of multifactorial inheritance.³ If this is so, then the careful separation of cases of glaucoma secondary to pseudoexfoliation of the lens capsule (PXF), trauma or cyclitis may display these genetic markers more clearly. Further there may be genetic differences between chronic open angle glaucoma (COAG), with cupping and field defects, and ocular hypertension, where cupping and field loss have not developed in spite of raised intraocular pressure. Similarly genetic differences may exist in low tension glaucoma, where cupping and field loss have developed in patients with normal pressure. If such genetic differences do exist, they may have diagnostic and prognostic value.

Most recognisable genetic inheritance in man, if not specifically pathogenetic, concerns blood groups. The relative frequencies of the ABO blood groups, the hereditary presence or absence in the saliva of the

individual's ABO blood group antigen or ABH secretion or non-secretion, and the ability or inability to taste certain thyroid-inhibiting derivatives of thiourea, such as phenylthiourea (PTC), are indicators of genetic associations. The dominantly inherited genes responsible for the ability to secrete the A, B, or O antigen in the saliva are not linked to the ABO genes.⁴ Such genetic associations would be of diagnostic value, particularly if there are differences between the various types of glaucomas. ABO and H antigens are found in the saliva of secretors but are not present in non-secretors. The ability to secrete these antigens is inherited in a straightforward dominant manner and may be associated with various diseases.⁴

To investigate these genetic associations, patients were investigated in the Glaucoma Investigation and Research Unit during 1983 to 1984, and their ABO and rhesus blood groups, ABH secretor, and PTC tasting status were determined. Particular attention was paid to precise diagnosis of the type of glaucoma so that any specific genetic associations could be identified. In particular, secondary glaucomas were considered separately, whether due to PXF, trauma,

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or cyclitis. A distinction was made between COAG with cupping and field loss, ocular hypertension with neither of these, and low tension glaucoma. A group of patients with large cups of the optic disc but no field loss and normal pressure was also examined. Angle closure glaucoma was separated into acute and chronic subgroups.

Materials and methods

In all new patients attending the Glaucoma Investigation and Research Unit during 1983–4 blood grouping was performed for the ABO blood groups and rhesus groups; secretor status was determined⁴ and phenylthiourea (1:50 000) tasting was performed.

Patients classified as ocular hypertensive had a pressure greater than 22 mmHg with no field loss or cupping of the optic disc. In chronic open angle glaucoma patients showed a typical field defect and pathological cupping of the optic disc with a pressure greater than 22 mmHg. Patients with low tension glaucoma showed similar field defects and cupping of the optic disc with a pressure which never rose above 22 mmHg. Cases of PXF, traumatic glaucoma, uveitic glaucoma, and acute or chronic angle closure glaucoma showed the typical physical signs of these conditions.

Statistical analysis of the data was by the χ^2 test.

Results

We examined 158 patients with ocular hypertension, 130 with COAG and 53 with low tension glaucoma. We also examined 55 patients with PXF with glaucoma, 14 with PXF with ocular hypertension, nine with PXF with no ocular hypertension, 10 with traumatic glaucoma, 11 with secondary uveitic glaucoma, 20 with acute angle closure glaucoma, 23 with chronic angle closure, and nine with neovascular glaucoma following central retinal vein thrombosis. The results were compared with those from 125 normal, age-matched control subjects and with the blood group distribution in 13 805 blood donors of the Red Cross Blood Bank of Victoria⁵ over the same period of time, whose ethnic composition was the same as our group of patients. We examined a further 28 patients with no glaucoma but with cup disc ratio greater than 0.6.

There was no significant difference between our controls and those of the Blood Bank nor between the controls and those without glaucoma but with cup disc ratio greater than 0.6.

BLOOD GROUPS

There were no significant differences between any of the groups studied in the relative frequencies of the

Table 1 Blood group results

	A	B	O	AB	Rh+	Rh-
Normal controls	47	19	54	5	109	16
Red Cross Blood Bank (%)	39	11	46	4	82	18
No glaucoma C/D>0.6	9	5	13	1	25	3
Ocular hypertension (OHT)	73	11	69	5	134	24
Chronic open angle glaucoma	53	12	61	4	113	17
Low tension glaucoma	20	8	21	4	48	5
Pseudoexfoliation with glaucoma	21	7	27	0	48	7
Pseudoexfoliation with OHT	5	5	6	0	14	2
Pseudoexfoliation, no OHT	7	0	2	0	9	0
Traumatic glaucoma	3	2	3	2	9	1
Secondary uveitic glaucoma	3	2	3	2	9	1
Acute angle closure glaucoma	9	2	8	1	14	6
Chronic angle closure glaucoma	13	2	8	0	22	1
Neovascular glaucoma	1	2	5	1	8	1

C/D=cup/disc ratio.

ABO blood groups (Table 1). There was also no significant difference in the relative frequency of any of the ABO groups in the 310 patients suffering from glaucoma compared with normal controls ($\chi^2=2.76$, 3 DF, $0.50>p>0.30$). However, there was a significant decrease in the number of Rh-negative patients in chronic angle closure glaucoma compared with acute angle closure glaucoma ($\chi^2=5.24$, 1 DF, $p<0.05$).

SECRETOR STATUS

The results of secretor status studies are shown in Tables 2 to 4. The secretors are compared with non-secretors in Table 2. There were fewer secretors in patients with ocular hypertension than in our normal controls ($\chi^2=5.68$, 1 DF, $p<0.02$) and the Blood Bank controls ($\chi^2=12.08$, 1 DF, $p<0.01$). There were also significantly fewer secretors among patients with ocular hypertension than among those with COAG

Table 2 Secretor status results

	Secretors (number of patients)	Non-secretors
Normal controls	99	23
Red Cross Blood Bank (%)	80	20
No glaucoma C/D>0.6	27	5
Ocular hypertension (OHT)	107*	49
Chronic open angle glaucoma	103	26
Low tension glaucoma	37	11
Pseudoexfoliation with glaucoma	44	10
Pseudoexfoliation with OHT	14	2
Pseudoexfoliation, no OHT	6	3
Traumatic glaucoma	9	1
Secondary uveitic glaucoma	11	1
Acute angle closure glaucoma	11	8
Chronic angle closure glaucoma	18	5
Neovascular glaucoma	6	3

*Significant to $p<0.01$ compared with normal controls ($\chi^2=5.68$, 1 DF, $p<0.02$) and Blood Bank controls ($\chi^2=12.08$, 1 DF, $p<0.01$).

Table 3 Secretor group results

	Secretor group (number of patients)						
	AH	H	HB	AB	ABH	A	B
Normal controls	38	39	18	0	4	0	0
No glaucoma C/D>0.6	7	11	5	0	0	0	0
Ocular hypertension (OHT)	51	43	10	0	2	0	1
Chronic open angle glaucoma	44	48	5*	0	3	0	3
Low tension glaucoma	15	17	4	1	0	0	0
Pseudoexfoliation with glaucoma	12	24	6	1	0	1	0
Pseudoexfoliation with OHT	4	4	5	0	1	0	0
Pseudoexfoliation, no OHT	4	2	0	0	0	0	0
Traumatic glaucoma	3	2	2	0	2	0	0
Secondary uveitic glaucoma	3	2	4	0	2	0	0
Acute angle closure glaucoma	4	5	2	0	0	0	0
Chronic angle closure glaucoma	9	7	2	0	0	0	0
Neovascular glaucoma	1	2	1	1	0	0	1

*Significant compared with normal ($\chi^2=11.78$, 4 DF, $p<0.02$).

($\chi^2=4.65$, 1 DF, $p<0.05$) and all the patients with glaucoma considered as a whole ($\chi^2=5.58$, 1 DF, $p<0.02$).

The secretor subgroups are shown in Table 3. There were significantly fewer HB secretors in patients with COAG than the normal controls ($\chi^2=11.78$, 4 DF, $p<0.02$). Ocular hypertensives had an incidence of HB secretors intermediate between normal patients and those with COAG, but this difference was not statistically significant.

The patients with PXF and raised intraocular pressure included fewer AH secretors and more HB secretors than those with COAG ($\chi^2=8.35$, 1 DF, $p<0.01$) (Table 4).

The secretor status of secondary glaucoma also differed from COAG, with an increase in HB and decrease in AH secretors in secondary glaucoma, whether angle closure glaucomas were included ($\chi^2=20.04$, 7 DF, $p<0.01$) or not ($\chi^2=31.89$, 7 DF, $p<0.01$).

Comparing all the cases of glaucoma as a whole, we found no significant difference from the controls in the relative frequency of ABH secretors and non-secretors ($\chi^2=0.34$, 1 DF, $0.70>p>0.50$).

Table 4 Secretor profiles for pseudoexfoliative glaucoma (PXF) and pseudoexfoliation with ocular hypertension (PXFOHT) compared with chronic open angle glaucoma (COAG)

	Secretor group (number of patients)						
	AH	H	HB	AB	ABH	A	B
PXFG and PXFOHT (58)	16	28	11	1	1	1	0
COAG (103)	44	48	5	0	3	0	3

Significant difference in AH and AB secretors in PXFG and PXFOHT compared with COAG ($\chi^2=8.35$, 1 DF, $p<0.01$).

Table 5 Taster status results

	Tasters	Non-tasters
Normal controls	44	76
No glaucoma C/D>0.6	8	17
Ocular hypertension (OHT)	46	105
Chronic open angle glaucoma	43	82
Low tension glaucoma	17	31
Pseudoexfoliation with glaucoma	16	39
Pseudoexfoliation with OHT	5	7
Pseudoexfoliation, no OHT	2	7
Traumatic glaucoma	6*	3
Secondary uveitic glaucoma	6†	3
Acute angle closure glaucoma	5	15
Chronic angle closure glaucoma	12	9
Neovascular glaucoma	4	5

*Significant compared with normal controls ($\chi^2=24.8$, 1 DF, $p<0.01$). †Significant compared with normal controls ($\chi^2=4.8$, 1 DF, $0.05>p>0.02$).

TASTER STATUS

The results are shown in Table 5. Patients who were tasters were significantly more common among those with traumatic glaucoma than among normal controls ($\chi^2=24.8$, 1 DF, $p<0.01$) and secondary uveitic glaucoma ($\chi^2=4.8$, 1 DF, $0.05>p>0.02$).

Discussion

This study supports the presence of certain genetic markers which distinguish some patients with COAG from normal controls and from patients with ocular hypertension. Thus patients with COAG had a significantly lower incidence of HB secretors than normal controls, with an incidence for ocular hypertensives intermediate between normal subjects and those with COAG. There were fewer ABH secretors in ocular hypertension than in patients with COAG and also fewer than in the normal controls.

Therefore normal patients who are HB secretors are much less likely to develop glaucoma. If such patients develop ocular hypertension, they are less likely than other patients to proceed to the development of cupping and field loss. The lower incidence of ABH secretors in ocular hypertension compared with COAG and normal persons suggests there is a genetic difference between some patients who develop ocular hypertension and do not go on to cupping and field loss and those who do.

The patients with PXF and raised intraocular pressure had a lower incidence of AH secretors and a higher incidence of HB secretors than those with COAG, their incidence resembling that of normal patients. This is compatible with previous work which suggested that the rise in pressure in PXF is secondary to the presence of the PXF material occurring in otherwise normal eyes not predisposed to glaucoma.⁶ Further, in cases of unilateral PXF with

a raised intraocular pressure a significant difference in cup disc ratio between affected and unaffected eyes has been reported; the increased cupping followed the development of raised intraocular pressure due to deposition of PXF.⁷

When all cases of secondary glaucoma as a group were compared with those with COAG, there was also a higher frequency of HB secretors and a lower frequency in AH secretors whether angle closure glaucomas were included or not. This confirms a genetic difference between some patients with COAG and those with secondary glaucoma like that noted for PXF.

Of less importance—patients who were tasters of phenylthiourea were more common among patients with traumatic and secondary uveitic glaucomas than among normal people. It has previously been noted that the fellow eyes of eyes with traumatic glaucoma have some increase of pressure, and therefore some patients are more likely to develop a rise in pressure after severe contusion injury,^{8,9} being different from the normal population.

We observed an association between ocular hypertension and non-secretion of ABH but not between COAG and non-secretion of ABH, although an association between non-secretors of ABH and primary glaucoma (open angle and narrow angle) has been reported from India.¹⁰

The familial incidence of chronic simple glaucoma and angle closure glaucoma has been emphasised by Miller,¹¹ and other workers have reported increased group A in open angle glaucoma,¹² of group O in congestive glaucoma,¹³ and of rhesus-positivity in open angle glaucoma,¹⁴ but we did not confirm a statistical association between the ABO blood groups and these glaucomas. Nor did we substantiate PTC tasting status as a marker for glaucoma, as shown by a previously reported¹⁵ raised incidence of non-tasters among patients with primary chronic simple glaucoma or tasters in patients with closed angle glaucoma.

Our failure to confirm some previously reported work emphasises that much of the work done on the genetic status of patients with glaucoma is conflicting. It should be remembered that statistical analysis indicates degrees of probability, and there may be genetic differences between population groups making comparison difficult.

We believe that the present study defines different types of glaucoma more carefully and may therefore be more likely to detect genetic differences, but few

were found. The study does suggest that the secretor status of patients with ocular hypertension may be helpful in determining which patients are more likely to progress to glaucoma. Unfortunately only a small proportion of patients are HB secretors, so the genetic markers we have described are only of limited usefulness in predicting which ocular hypertensive patients are likely to develop cupping and field loss. Perhaps more sophisticated studies of blood groups and subgroups will refine these tests further and make more comprehensive and precise prediction possible.

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