SCIENTIFIC REPORT

Systemic hypertension and glaucoma: mechanisms in common and co-occurrence

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Aims: To determine whether systemic hypertension and glaucoma might coexist more often than expected, with possible implications for treatment.

Methods: Case-control study using general practitioner database of patients with glaucoma matched with controls for age and sex.

Results: Hypertension was significantly more common in the 27 080 patients with glaucoma (odds ratio 1.29, 95% confidence intervals 1.23 to 1.36, $p<0.001$) than in controls. Treatment by oral β blockade appeared to protect from risk (odds ratio 0.77, 95% CI 0.73 to 0.83, $p<0.0001$), but oral calcium channel antagonists or angiotensin converting enzyme (ACE) inhibitors did not (odds ratios 1.34, 1.24 to 1.44 and 1.16 1.09–1.24, respectively, $p<0.0001$ in each case). Oral corticosteroid treatment was associated with enhanced risk (odds ratio 1.78, 1.61 to 1.96).

Conclusion: Common pathogenetic mechanisms in ciliary and renal tubular epithelia may explain coincidence of glaucoma and systemic hypertension. The choice of cardiovascular treatment, could substantially influence glaucoma incidence, with β blockade protecting and ACE inhibitors or calcium channel blockers not affecting underlying risk.

Hypertension is an important risk factor for cardiovascular disease, and glaucoma is a common cause of blindness. Recent data suggest common mechanisms related to altered epithelial sodium transport in the distal nephron and ciliated epithelium. Excessive renal sodium retention leads to systemic hypertension, and increased ciliary epithelial sodium transport leads to extrusion of sodium into the aqueous humour. In both, sodium transport is regulated by corticosteroid hormones (cortisol and aldosterone), and the human ciliary and distal nephron epithelia express the same effector mechanisms as corticosteroid receptors (GR and MR), pre-receptor metabolising enzymes, 11β-hydroxysteroid dehydrogenase (11β-HSD2)[1 2] and post-receptor ligands to affect sodium reabsorption (serum and glucocorticoid regulated kinase sgk, Na/K-ATPase, and epithelial sodium channel EnaC). If increased sodium reabsorption underpinned the occurrence of hypertension and glaucoma then an epidemiological link between the two should be demonstrable. We have used the General Practitioner Research Database (GPRD) to determine if the two diseases occur together more commonly than would be expected. β Blockade is an established oral method of treating raised blood pressure, and ocular method of treating glaucoma; we have therefore examined the possible association between the type of hypotensive treatment in use and the frequency of glaucoma diagnosis. Finally, if corticosteroid dependent mechanisms in common underlie the occurrence of hypertension and glaucoma then oral corticosteroid therapy would be expected to substantially increase glaucoma risk.

METHOD

After obtaining ethical approval the frequency of documented hypertension was sought in cases of glaucoma compared with age and sex matched controls in GPRD, a well characterised practice database in the United Kingdom, with some four million patients registered, including details of drugs prescribed and diagnoses coded. Data have been shown to record information accurately about clinical diagnoses,[3 4] and findings in GPRD have given similar results to other methods, in examining relations between drug treatment and outcome.[5 6] Preliminary inquiry suggested some 30 000 cases of glaucoma were registered on the database, so that, given a 10% prevalence of hypertension in the general population, some 3000 cases would be expected with both together by chance.

Cases

Information was abstracted about written diagnoses of hypertension, whatever the possible cause, with details of cardiovascular and corticosteroid treatment given in all cases of glaucoma diagnosed between 1 January 1990 and 31 December 1999.

Controls

Each glaucoma case was matched with one control for age, within 2 years, and sex, drawn randomly from the files of any of the participating general practitioners. Information for the same dates as those applying to the matched cases was sought, including details of treatments for high blood pressure, recorded information about abnormal blood pressure levels, and any treatments which would have been expected to be given if the control had glaucoma.

Definitions

Hypertension

Patients were defined as having hypertension if that OXMIS (Oxford Medical Information Systems) diagnosis code, alone or with a modifier, had been entered in their records. Blood pressure entries within records were coded as normal or abnormal. If abnormal then the readings on at least one occasion should have exceeded 179 mm Hg systolic and/or 99 mm Hg diastolic.

Glaucoma

Diagnoses of glaucoma were accepted as entered in records; 88% were current recipients of sympathomimetics, β blocking agents, prostaglandins, or carbonic anhydrase inhibitors, but no controls.

Abbreviations: ACE, angiotensin converting enzyme; GPRD, General Practitioner Research Database

Table 1 Diagnoses of hypertension and of raised blood pressure made in cases and controls

		Cases	Controls
Hypertension recorded			
Yes		3508	2794
No		23 572	24 286
Odds ratio			1.29
95% CI	1.23 to 1.36, p<0.001		
Blood pressure recorded			
Yes	abnormal	5870	4544
	normal	12 928	11 858
No		8282	10 678
Odds ratio comparing proportions recorded as normal and abnormal			1.19
95% CI	1.13 to 1.24, p<0.001		

Data for cases and controls recorded before diagnoses of glaucoma were made.

Hypotensive treatments

Four types were examined, being classified using *British National Formulary* categories, angiotensin converting enzyme (ACE) inhibitors (category 2.5.5.1), β blocking agents (2.4), calcium channel antagonists (2.6.2), and diuretics. (2.2.1 and 2.2.2). Because hypotensive treatments have other uses we analysed irrespective of the underlying cardiovascular condition, and then examined association with the type of drug in use where a diagnosis of hypertension had or had not been made.

Analysis

Odds ratios with 95% confidence intervals were calculated examining observed and expected numbers with and without diagnosed hypertension or raised blood pressure in patients with glaucoma compared with controls. Univariate analyses examined possible associations with the type of hypotensive therapy in use and with oral corticosteroid therapy. For these analyses all diagnoses of hypertension were made before diagnoses of glaucoma. Drug treatments were considered as current if prescribed in the 1–90 days before glaucoma diagnosis and as ever used if prescribed at any time in the previous 1–1095 days.

RESULTS

A total of 27 080 patients in the database had recorded glaucoma and were successfully matched with controls; all diagnoses, except 121 (0.45%) were made between 1990 and 1999 inclusive. Table 1 shows that hypertension was recorded significantly more often in individuals later found to have glaucoma. Use of recorded abnormal blood pressure readings gave similar results, both being highly significant (p<0.001).

Table 2 shows that the likelihood of glaucoma being diagnosed was significantly reduced in current users of oral β blocking agents, whether hypertensive or not (p<0.0001), odds ratios returning close to unity in ever users.

By contrast, odds ratios were significantly raised in current takers of ACE inhibitors, and calcium channel antagonists (p<0.0001 in both cases), and remaining raised in ever users. Concurrent use of diuretics did not materially alter findings. The odds ratio comparing the risk of glaucoma in all takers of diuretics, irrespective of any co-treatment, and all non-takers, was raised slightly, but more in ever users than current users.

Table 3 gives data according to cardiovascular treatment received, in patients with and without hypertension. Glaucoma was diagnosed less often than expected in current takers of β blocking agents but not in ever takers, while ever and current takers of ACE inhibitors and calcium channel blocking agents tended to be at similar raised risk.

Table 4 shows that takers of oral corticosteroids were significantly more likely to be diagnosed as having glaucoma than non-takers, and that the relation was stronger in the more recent takers (p<0.0001).

Table 2 Oral cardiovascular drug treatment in all patients whether hypertensive or not, with diagnoses of glaucoma and in controls (all treatments given before glaucoma diagnoses)

	Hypertension treatment					
	1–1095 days before			1–90 days before		
	Yes	No	Odds ratio (95% CI)	Yes	No	Odds ratio (95% CI)
β Adrenergic blocking agents						
Minus diuretic	2037	2171	0.97	1357	1704	0.77*
Plus diuretic	1515	1488	(0.92 to 1.02) p=0.2	536	680	(0.73 to 0.83) p<0.0001
ACE inhibitors						
Minus diuretic	805	604	1.30	910	659	1.34*
Plus diuretic	1454	1182	(1.21 to 1.38) p<0.0001	850	683	(1.24 to 1.44) p<0.0001
Calcium channel blockade						
Minus diuretic	1475	1331	1.18	1477	1331	1.16*
Plus diuretic	1840	1549	(1.12 to 1.25) p<0.0001	926	801	(1.09 to 1.24) p<0.0001
All diuretic users						
Use	6695	6170	1.13	4570	4303	1.08
Non-use	20 385	20 910	(1.08 to 1.18) p<0.0001	22 510	22 777	(1.03 to 1.14) p<0.002

*Aggregate value summing numbers for diuretic users and non-users. Probability values compared with non-use.

Table 3 Oral prescriptions for β blocking agents, ACE inhibitors, and calcium channel antagonists in patients with and without later glaucoma

	Treatment period before glaucoma diagnosis							
	1–1095 days				1–90 days			
	Yes	No	Odds ratio*	95% CI	Yes	No	Odds ratio*	95% CI
(A) In patients with diagnoses of hypertension and/or recorded raised blood pressure								
No diuretics								
β blockade	908	858	1.06	0.96 to 1.17 p=0.2	713	785	0.90	0.82 to 1.00 p=0.6
ACE inhibitors	600	458	1.32	1.17 to 1.49 p<0.0001	706	496	1.44	1.28 to 1.61 p<0.0001
Calcium channel antagonists	765	620	1.24	1.11 to 1.38 p<0.0001	858	672	1.29	1.16 to 1.42 p<0.0001
With diuretics								
β blockade	1018	947	1.08	0.99 to 1.18 p=0.1	326	422	0.77	0.67 to 0.89 p<0.0005
ACE inhibition	1031	738	1.41	1.28 to 1.56 p<0.0001	558	390	1.44	1.26 to 1.64 p<0.0001
Calcium channel antagonists	1170	910	1.30	1.19 to 1.42 p<0.0001	562	437	1.29	1.14 to 1.47 p<0.0001
(B) In patients without diagnoses of hypertension or recorded raised blood pressure								
No diuretics								
β blockade	836	970	0.86	0.78 to 0.94 p=0.0015	472	698	0.67	0.60 to 0.75 p<0.0001
ACE inhibitors	160	114	1.41	1.11 to 1.79 p=0.006	166	129	1.29	1.02 to 1.62 p=0.4
Calcium channel antagonists	532	526	1.01	0.90 to 1.14 p=0.9	468	461	1.02	0.89 to 1.16 p=0.8
With diuretics								
β blockade	377	396	0.95	0.83 to 1.10 p=0.5	168	199	0.84	0.69 to 1.04 p=0.1
ACE inhibitors	303	314	0.97	0.82 to 1.13 p=0.7	206	214	0.96	0.79 to 1.17 p=0.7
Calcium channel antagonists	512	430	1.19	1.05 to 1.36 p=0.008	279	257	1.09	0.92 to 1.29 p=0.4

*Odds ratios calculated as use against non-use.

DISCUSSION

Diagnoses of glaucoma were more likely to be made in patients with hypertension than in those without raised blood pressure. Odds ratios were low, but the numbers on which calculations are based are large and confidence intervals tight, so that findings are unlikely to be the result of chance. The tendency for glaucoma and hypertension to co-exist is plausible, fitting with concepts of common causal mechanisms, through modulation of sodium transport at receptors in ciliary and renal tubular epithelia,[7] and agrees with the findings of others.[8]

Dysfunctional corticosteroid control of epithelial sodium transport in the distal nephron is seen in several monogenic diseases, including glucocorticoid remediable hyperaldosteronism (a cause of aldosterone excess), apparent mineralocorticoid excess, where cortisol acts as mineralocorticoid in the absence of 11β-HSD, and Liddle's syndrome caused by activating mutations in EnaC.[9] In the broader hypertensive population, primary aldosteronism is being advocated as a common cause of essential hypertension,[10] and approximately 40% of such patients have reduced plasma renin activity, in keeping with enhanced renal sodium reabsorption.

The ciliary epithelium, another corticosteroid target, acts as an ''inverted'' epithelium producing aqueous humour through sodium transport. It also expresses mineralocorticoid and glucocorticoid receptors, and 11β-HSD, together with EnaC.[11–14] Our recent data have additionally shown corticosteroid regulation of sgk in the ciliary epithelium.[14] Administration of aldosterone to rabbits increases intraocular pressure, while spironolactone, a mineralocorticoid antagonist, and mefipristone (RU38486), a glucocorticoid antagonist,[15 16] lower pressure. Furthermore, intraocular pressure is raised in Cushing's syndrome[17] and up to 40% of patients taking glucocorticoid therapy develop raised intraocular pressure.[17–19] The data in table 4 indicates an extra 500–600

Table 4 Oral corticosteroid prescription in patients with glaucoma and in controls

	Period before glaucoma diagnosis					
	1–1095 days			1–90 days		
			Odds ratio			Odds ratio
	Yes	No	95% CI	Yes	No	95% CI
Taking corticosteroids						
Yes	2778	2038	1.41* (1.32 to 1.49)	1135	651	1.78* (1.61 to 1.96)
No		24 302	25 042		25 945	26 429

*p<0.0001.

cases of glaucoma occur in recipients of oral corticosteroids in the population studied, equivalent to some 9000 overall in the United Kingdom.

An association between glaucoma and hypertension might be found because of particular attention to the possible retinal adverse effects of hypertension, a phenomenon in keeping with Berkson's bias.[20] However, our findings of differential risk of glaucoma in takers of ACE inhibitors and calcium channel blocking agents, from those taking β blocking agents, are difficult to explain through bias. Lowered risk of glaucoma in takers of oral β blocking agents is clinically plausible, and supported by reduced risk in current, but not ever takers but our data do not allow us to determine whether any particular glaucoma type, notably primary open angle, is responsive. Raised odds ratios in takers of ACE inhibitors or calcium channel blocking agents are likely to represent failure to protect against a commonly associated disease, rather than increased risk caused by treatment because odds ratios were virtually identical in known current takers and ever takers of these drugs.

GPRD has a catchment population of some four million and, assuming equivalent disease incidence elsewhere in the United Kingdom, there would be about 15 times 27 000 cases of glaucoma in the United Kingdom, or some 400 000 cases overall, of whom about one fifth, or 80 000 would be expected to be hypertensive. Substantial numbers would be receiving treatment by oral blockade, with possible beneficial change in glaucoma behaviour.

We conclude that systemic hypertension and glaucoma tend to be associated, that common mechanisms related to sodium handling are responsible, and that systematic treatment with corticosteroids and by β blockade may have clinically important and opposite effects on glaucoma risk.

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Ethical approval was obtained from the ethics committee responsible for GPRD.

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