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Association of primary open-angle glaucoma with systemic hypertension

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ABSTRACT

Introduction: Open-angle glaucoma is a slowly progressive neurodegeneration of retinal ganglion cells and their axons characterized by a specific pattern of optic nerve head and visual field damage. Glaucoma is probably one of the most prominent ocular outcomes of systemic hypertension (HTN). In the light of foregoing background and considering glaucoma having probable association with systemic HTN, the present study was undertaken. **Materials and Methods:** This study was done in a tertiary care hospital over a period of 18 months, after the ethical clearance and informed written consent of the patients. All individuals above 40 years of age regardless of gender were included in the study. Included patients underwent detailed ocular and systemic history and detailed examination which included visual acuity by Snellen drum, refraction, intraocular pressure by Schiotz tonometer, gonioscopy using Zeiss four-mirror lens to evaluate the anterior chamber, visual field changes seen by Humphrey field analyzer, slit-lamp examination, fundus evaluation by both direct and indirect ophthalmoscopy, and 90D lens with special attention to glaucomatous fundus changes using optical coherence tomography (OCT) with Cirrus SD OCT Carl Zeiss Meditec. Apart from ocular examination, patient's blood pressure was taken with sphygmomanometer, and demographic and anthropometric details were also noted. **Result:** A case-control study was conducted on 510 individuals of age 40 years and above, irrespective of sex. Out of them, 340 (66.7%) patients were hypertensives with systemic blood pressure of >140/90 mmHg, whereas 170 (33.3%) patients were non-hypertensives so were taken as controls. On looking for the presence of glaucoma in both the groups, it was observed that 13.8% of cases and 5.9% of controls had signs of glaucoma (P = 0.003, χ^2 = 8.58). On the further distribution of glaucoma into established and preclinical type, we found that 53.19% of glaucomatous cases and 70% of glaucomatous controls had established glaucoma (P = 0.150), while 46.8% and 30% were having preclinical glaucoma, respectively (P = 0.020). **Conclusion:** A positive association was seen between HTN and primary open-angle glaucoma (POAG) prevalence. A significant difference in the distribution pattern of different clinical signs of POAG between hypertensives and controls was observed. The findings show that regardless of pathophysiology operating for development of glaucoma, the clinical manifestation does not vary significantly between normotensives and hypertensives. Optic disc changes and as a result field changes are more pronounced among hypertensives as compared to normotensives, though the analysis statistically is not significant. Thus, patients of systemic HTN are at high risk of glaucoma as HTN is contributing to both physiological as well as pathological damage.

Key words: Open-angle glaucoma, systemic hypertension, normotensives

INTRODUCTION

Open-angle glaucoma is a slowly progressive neurodegeneration of retinal ganglion cells and their axons characterized by a specific pattern of optic nerve head and visual field damage.[1] Primary open-angle glaucoma (POAG) occurs in the elderly, rarely seen earlier than 40 years of age, and tends to run in families. Its inheritance is multifactorial and polygenic.[2]

India accounts for a minimum of 12.9% of POAG blindness in the world, and these figures are expected to be doubled by 2020 AD.[3]

Hypertension (HTN) has a definitive cardiovascular impact; however, it also affects the ocular system which is manifested in various forms. Glaucoma is probably one of the most prominent ocular outcomes of systemic HTN. In the recent years, the ongoing researches have suggested that common mechanisms related to altered epithelial sodium transport in the distal nephron and ciliary epithelium lead to emergence of both systemic HTN as well. Having the common pathophysiology, it is expected that systemic HTN and glaucoma might coexist or have a cause-effect relationship.

Studies investigating the relationship between systemic HTN and glaucoma have shown variable degree of association. However, a direct and clear relationship between glaucomatous damage and blood pressure level has yet not been established.[4]

In the light of foregoing background and considering glaucoma having probable association with systemic HTN, the present study was undertaken.

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MATERIALS AND METHODS

This study was done in a tertiary care hospital over a period of 18 months, after the ethical clearance and informed written consent of the patients. It was a cross-sectional case-control study done with an aim to find the prevalence of established cases of POAG in systemic hypertensives.

All individuals above 40 years of age regardless of gender who attended the eye outpatient department were included in the study. All those who were found to have secondary glaucoma, established cause of glaucoma, uveitis, corneal scarring, or optic atrophy due to other causes were excluded from the study.

Included patients underwent detailed ocular and systemic history and detailed examination which included visual acuity with and without pinhole by Snellen's drum, refraction, intraocular pressure (IOP) by Schiotz tonometer, gonioscopy using Zeiss four-mirror lens to evaluate the anterior chamber, visual field changes seen by Humphrey field analyzer (HFA) using 30-2 program (version 40), slit-lamp examination, fundus evaluation by both direct and indirect ophthalmoscopy, and 90D lens with special attention to glaucomatous fundus changes using optical coherence tomography (OCT) with Cirrus SD OCT Carl Zeiss Meditec.

Apart from ocular examination, patient's blood pressure was taken with sphygmomanometer, and demographic and anthropometric details were also noted.

Patients were categorized into two groups as cases and controls based on their systemic blood pressure level in accordance with the definition and guidelines by JMC-7 in 2003. It defines HTN as a persistent elevation of blood pressure >140/90 mmHg. Both groups were subjected to similar evaluation protocol on a pre-set pro forma.

Statistical analysis was done using the Statistical Package for Social Sciences Version 20.0 Chi-square test was used for comparison of categorical data. The confidence level of the study was kept at 95%. $P < 0.05$ was taken as statistically significant value.

OBSERVATION AND RESULTS

A case-control study was conducted on 510 individuals of age 40 years and above, irrespective of sex. Out of them, 340 (66.7%) patients were hypertensives with systemic blood pressure of >140/90 mmHg, whereas 170 (33.3%) patients were non-hypertensives so were taken as controls. In both the groups, maximum patients were in the age group of 50-59 years. Among the hypertensive patients, the majority (85%) had systolic blood pressure (SBP) within the range of 140-150 mmHg with a ratio of 2:1 and 1.2:1, respectively, in cases and controls.

On looking for the presence of glaucoma in both the groups, it was observed that 13.8% of cases and 5.9% of controls had signs of glaucoma ($P = 0.003$, $\chi^2 = 8.58$). On he further distribution of glaucoma into established and preclinical type, we found that 53.19% of glaucomatous cases and 70% of glaucomatous controls had established glaucoma ($P = 0.150$) while 46.8% and 30% were having preclinical glaucoma, respectively ($P = 0.020$) [Table 1].

We looked for the various diagnostic clinical signs in established POAG patients, for which POAG cases were divided into four groups such as A (increased IOP + glaucomatous field changes), B (increased IOP + glaucomatous disc changes), C (field + disc changes), and D (IOP + disc + field changes) and found that the distribution pattern of POAG diagnostic signs in controls and hypertensive cases was statistically insignificant ($P = 0.851$) [Table 2].

Table 3 shows the different range of IOP distribution among various blood pressure groups. The difference was found to be statistically insignificant among hypertensive cases ($\chi^2 = 4.602$; $P = 0.128$).

On disc damage likelihood scale (DDLS) grading scale, the difference in optic disc changes among various SBP levels of hypertensive cases was found to be statistically significant ($\chi^2 = 1.48.19$, $P \leq 0.001$). When severity range of POAG based on visual field by HFA: Hodapp grading was assessed, we found that 2.9% of cases had moderate glaucoma, 1.5% had mild, and 1.5% had severe glaucoma, whereas in controls, only 2.4% had mild glaucoma and 1.2% had moderate. However, the difference in severity proportion of POAG between cases and control was statistically insignificant ($\chi^2 = 4.09$; df = 2; $P = 0.129$) [Tables 4 and 5].

DISCUSSION

HTN is a widely recognized risk factor for cardiovascular disease. Systemic HTN has been shown to be caused by excessive renal sodium retention. Excessive retention of sodium in nephrons in turn agitates the ciliary epithelium, and this in turn leads to extrusion of sodium into the aqueous humor,[5] thus resulting into an increase in IOP which is a recognized risk factor and manifestation of POAG.

This defined physiological relationship leads us to an immediate inference that systemic HTN might be responsible for increase in IOP and as a result in the development of POAG. Although the relationship between systemic HTN, IOP, and glaucoma has been studied by various workers[6-9] with various perspectives, the relationship still remains to be understood clearly.

As a matter of fact, glaucoma is not seen in every patient of systemic HTN, similarly every patient of glaucoma does not have systemic HTN, thus the relationship between systemic HTN and glaucoma is governed by other factors too which are required to be examined in varied perspectives. The present study was

Table 1: Distribution of established and preclinical POAG

Stage of POAG	Study group		χ^2	*P*
	Controls *n*=170 (%)	HTN cases *n*=340 (%)		
Established glaucoma	7 (4.1)	25 (7.4)	2.02	0.156
Preclinical glaucoma	3 (1.8)	22 (6.5)	5.38	0.020
Total	10 (5.9)	47 (13.8)	7.20	0.007

Prevalence of preclinical glaucoma is statistically significantly high in hypertensive cases (χ^2=5.38; *P*=0.020). HTN: Hypertension, POAG: Primary open-angle glaucoma

Table 2: Distribution of POAG diagnostic clinical signs in established POAG cases

Study group	Group				Total
	A	B	C	D	
	Glaucoma diagnostic signs				
	↑IOP + glaucoma field changes	↑IOP + glaucoma disc changes	Field + disc changes	IOP + disc and field changes	
HTN cases *n*=340 (%)	12 (48.0)	5 (20)	2 (8)	6 (24)	25
Controls *n*=170 (%)	4 (57.1)	1 (14.3)	0	2 (28.6)	7

The difference in distribution pattern of POAG diagnostic signs in controls and HTN cases is statistically insignificant (χ^2=0.792, *P*=0.851). HTN: Hypertension, POAG: Primary open-angle glaucoma

Table 3: SBP versus IOP

Study group	IOP range				
	10-21mmHg	21-30 mmHg	30-40 mmHg	40-50 mmHg	>50 mmHg
HTN cases	309	18	7	4	2
<140 (controlled on medication) *n*=11 (%)	8 (72.7)	2 (18.2)	0 (0)	1 (9.1)	0 (0)
140-160 *n*=289 (%)	264 (91.3)	14 (4.8)	7 (2.4)	2 (0.7)	2 (0.7)
>160 *n*=40 (%)	37 (92.5)	2 (50)	0 (0)	1 (2.5)	0 (0)
Control					
<140 (%)	158 (92.9)	11 (6.5)	1 (0.6)	0	-

There is a significant difference in IOP range distribution between cases and control (χ^2=17.952; df=3; *P*<0.001). There is insignificant difference in IOP range distribution among various blood pressure group of hypertensive cases (χ^2=12.602; *P*=0.128). *Percentages have been calculated row wise. SBP: Systolic blood pressure, IOP: Intraocular pressure, HTN: Hypertension, POAG: Primary open-angle glaucoma

undertaken with an aim to find the prevalence of preclinical and established cases of POAG in patients with systemic HTN, to ascertain whether systemic HTN is a risk factor for developing POAG, and to study whether SBP can be taken as a guide in predicting occurrence/presence of POAG.

For the purpose, an exploratory study was carried out using a case-control study design in which a total of 340 individuals known to have systemic HTN were enrolled as cases and a total of 170 subjects not having systemic HTN were taken as controls. In the present study, although the majority of cases as well as controls were males, the proportion of males in case group was higher (65.6%) as compared to that in control group (54.1%). According to Lewallen and Courtright,[10] although controls must be like the cases in many ways, it is possible to overmatch. Overmatching can make it difficult to find enough controls. Furthermore, once a matching variable has been selected, it is not possible to analyze it as a risk factor. Thus, in the present study, gender of patients was a possible confounder and thus remains a limitation.

Maximum number of cases in the study were in the age group of 50-59 years (48.4%). As both HTN as well as POAG occur in the elderly, rarely seen earlier than 40 years of age,[11] therefore, more than 40 years of age was the moderate criteria for selection of patients. In their study, He *et al*.[12] also found maximum number of their patients in 50-59 years of age. In the present study, the overall prevalence of POAG (established as well as preclinical) was 13.8% among hypertensive cases and only 5.9% among normotensive controls. On evaluating this data statistically, the difference was found to be significant (*P* = 0.007). Thus, a positive association was seen between HTN and POAG prevalence. Similar to results of the present study, Tielsch *et al*.[13] showed a positive association between blood pressure and POAG. In another study, Dielemans *et al*.[14] showed that HTN was associated with an odds ratio of 2.33 (95% confidence interval [CI]: 0.99-5.47) for high-tension glaucoma. In the present study, we observed these odds to be 2.57 (95% CI: 1.26-5.22) among hypertensives for any type of POAG. Mitchell *et al*.[15] also found hypertensive patients to have an odds ratio of 1.51 for OAG. The relationship between glaucoma and HTN has also been established by other workers.[5,16-18] The findings of the present study endorsed these observations.

We did not observe any significant difference in the distribution pattern of different clinical signs of POAG between hypertensives and controls. The findings show that, regardless of pathophysiology operating for development of glaucoma, the clinical manifestation does not vary significantly between normotensives and hypertensives. Although there are varied pathophysiological mechanisms describing glaucoma, each one of them is not dependent on increase in systemic blood pressure as a reason for glaucoma development. However, hypertensive patients have additional mechanisms guiding to development of glaucoma, thus leading to an additional burden of POAG as observed in the present study.

In the present study, only 0.6% controls had IOP >30 mm Hg, whereas among hypertensive cases, as many as 3.8% of patients had IOP >30 mmHg, thus suggesting the fact that HTN and as such incremental blood pressure is responsible for phenomenal rise in IOP. The higher SBP is responsible for increase in IOP, and in turn, this ocular HTN has been shown to be responsible for optic disc changes.[19,20] The observation in our study is in line with observations described in the previous works that each 10 mmHg increment in SBP leads to an increase in IOP.[21-24] However, in the present study, we failed to establish any such linear relationship.

Evaluation analysis of glaucomatous changes in optic disc in relation to levels of SBP revealed that overall disc size remains

Table 4: Optic disc changes in hypertension cases in relation to level of SBP (DDLS grading)

Optic disc changes (DDLS grade)	SBP range								Total
	<140 mmHg *n*=11 (%) (cases on medication)			140-160 mmHg *n*=289 (%)			>160 mmHg *n*=40 (%)		*n*=340 (%)
	Size of disc (mm)								
	Small (<1.5)	Average (1.5-2.0) *n*=11 (%)	Large disc (>2.0)	Small (<1.5)	Average (1.5-2.0) *n*=285 (%)	Large disc (>2.0) (%)	Small (<1.5)	Average (1.5-2.0) *n*=40 (%)	Large disc (>2.0)	
0a		6 (54.5)			118 (41.1)	3 (100)		18 (45)		145 (42.6)
0b		2 (18.2)			142 (49.8)			18 (45.0)		162 (47.6)
1		1 (9.1)			10 (3.5)			2 (5)		13 (3.8)
2		1 (9.1)			12 (4.2)			1 (2.5)		2 (0.6)
3				1 (100)	1 (0.4)					1 (0.3)
4					1 (0.4)					1 (0.3)
5		1 (9.1)								1 (0.3)
6										0
7					1 (0.4)			1 (2.5)		2 (0.6)

χ^2=148.19, df=12; *P*<0.001. The difference in optic disc changes among various SBP levels of hypertensive cases is statistically significant. SBP: Systolic blood pressure, DDLS: Disc damage likelihood scale

Table 5: Severity range of poag (based on visual field by HFA: Hodapp grading)

Severity of POAG	Cases *n*=340 (%)	Control *n*=170 (%)
Mild (< −6 dB)	5 (1.5)	4 (2.4)
Moderate (−6 to −12 dB)	10 (2.9)	2 (1.2)
Severe (>−12 dB)	5 (1.5)	0
Total	20 (5.9)	6 (3.5)

The difference in severity proportion of POAG between cases and control was insignificant (χ^2=4.09; df=2; *P*=0.129). POAG: Primary open-angle glaucoma, HFA: Humphrey field analyzer

within average range (1.5-2 mm) irrespective of SBP level. However, when analyzed possible glaucomatous changes in optic disc, graded on disc DDLS grading system; in relation to levels of SBP, in the present study, with SBP <140 mmHg due to medications, only three patients had DDLS Grade 1 or above glaucomatous optic disc changes, whereas in those with SBP 140-160 mmHg and above, there were as many as 30 patients. These findings suggest that glaucomatous optic disc changes of higher order have a strong association with increased systemic blood pressure and as such the increased blood pressure is responsible for pathological changes in optic disc. Systemic HTN as such may directly damage the small vessels of the optic disc[25] and thus bring about changes in optic disc.[10]

In accordance with above observations, we also found that severity of POAG is significantly more in hypertensives as compared to those having SBP ≤140 mmHg. Based on visual field by HFA: Hodapp grading, we found that as many as 15/20 (75%) of hypertensives had moderate-to-severe glaucoma, whereas in normotensives, 4/6 (66.7%) patients had mild grade of glaucoma. These findings indicate that structural changes resulting in optic disc changes and as a result field changes are more pronounced among hypertensives as compared to normotensives, though the analysis statistically is not significant.

The foregoing discussion highlights that systemic blood pressure plays an important role in the pathophysiology of POAG. Although alternate mechanisms responsible for glaucoma and its progression are also functional and might be attributable for the development of POAG, yet systemic HTN alone seems to be one of the key player in determining the prevalence and severity of POAG. It can be concluded that patients of systemic HTN are at high risk of glaucoma as HTN is contributing to both physiological as well as pathological damage.

Although the present study had certain limitations and despite being conducted in a reasonably large sample, the findings suggest that relationship between POAG and HTN should be studied further in even larger sample size. It is recommended that ocular examination be taken as one of the key ingredients of glaucoma control strategy among hypertensives. Moreover, systemic blood pressure control should also be viewed as a strategy for glaucoma control. Further studies to have better understanding of pathophysiological mechanism as related to HTN are recommended.

CONCLUSION

A positive association was seen between HTN and POAG prevalence. A significant difference in distribution pattern of different clinical signs of POAG between hypertensives and controls was observed. The findings show that regardless of pathophysiology operating for development of glaucoma, the clinical manifestation does not vary significantly between normotensives and hypertensives. Optic disc changes and as a result field changes are more pronounced among hypertensives as compared to normotensives, though the analysis statistically is not significant. Thus, patients of systemic HTN are at high risk of glaucoma as HTN is contributing to both physiological as well as pathological damage.

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