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A STUDY ON SYSTEMIC RISK FACTORS FOR PRIMARY OPEN ANGLE GLAUCOMA

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ABSTRACT

Glaucoma is a major public health problem, causes irreversible visual impairment and is the most frequent cause of blindness in the world, second only to cataract. It is a 'silent killer' as most of the time; it is asymptomatic up to the very advanced stage. To assess the relationship between potential risk factors and the development of Primary open angle glaucoma.It was a case control study where, 134 cases of POAG and 134 normal individuals were enrolled. Study was carried out for 18 months from Dec 2011 to May 2013. History regarding age, gender, chronic tobacco intake, chronic alcohol intake, hypertension, diabetes, systemic corticosteroid intake, thyroid disease and family history of glaucoma was taken.Ocular examination like IOP measurement, Gonioscopy and Visual Field Charting was done. General evaluation included anthropometric measurements–height and weight (for BMI), blood pressure by sphygmomanometer, blood sugar estimation (Fasting & Post prandial) and thyroid function test. Odds ratio was calculated to estimate the risk.Higher BMI, chronic tobacco intake, known family history, Hypertension and Diabetes were proved as positive risk factors for POAG. Thyroid dysfunction, alcohol intake and chronic systemic steroid intake were not significantly associated with POAG.

Keywords: POAG, Risk factors, Hypertension, Diabetes mellitus, BMI, Tobacco intake

INTRODUCTION

Glaucoma, second only to cataract, is the most frequent cause of blindness in the world[1]. It is a major public health problem, causing irreversible visual impairment which hampers day to day work[2]. It is a 'silent killer' as most of the time, it is asymptomatic up to the very advanced stage and thus at the time of presentation, the visual loss is often irrecoverable[3,4]. Primary Open Angle Glaucoma (POAG) is defined as 'a progressive, chronic optic neuropathy where intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This is associated with an open anterior chamber angle[5]. POAG occurs in elderly, rarely seen earlier than 40 years of age and tends to run in families. Its inheritance is multi-factorial and polygenic[6]. About 60 million persons are estimated to be affected by glaucoma. Of these, an estimated 11.2 million cases are from the Indian subcontinent[7, 8]. Worldwide, over 2 million people develop POAG every year[9]. The reported prevalence for Primary Open Angle Glaucoma (POAG) varies between 1.62% and 3.51%[8]. The prevalence increases with age, and >90% are not aware of the disease[10]. Los Angeles Latino eye study found a prevalence of open angle glaucoma of 4.9% in the general population[11]. Several risk factors (viz. age, gender,

family history, obesity/body mass index, use of tobacco/alcohol, systemic steroid intake, hypertension, diabetes mellitus, thyroid disease) have been mentioned in literature for development and progress of POAG[12]; but a common consensus about certainty of several of them is still missing. The present study was conducted to assess the relationship between potential risk factors and the development of POAG.

MATERIALS AND METHODS

It was a hospital based case control study, carried out in the Department of Ophthalmology at Era's Lucknow Medical College and Hospital, Lucknow from Dec 2011 to May 2013. All patients of age 40 years and above regardless of sex; diagnosed as POAG were included in the study. The POAG was defined as: a person having glaucomatous field defect, glaucomatous disc changes or ocular pressure of ≥21 mm Hg in the presence of an open angle in either eye[6]. Patients having occludable angle in either eye or any history of intraocular surgery were excluded. Age and sex matched normal individuals not having POAG or any other debilitating eye pathology were taken as control. History regarding age, gender, chronic tobacco intake, chewable and smoked (≥10 pack years), chronic alcohol intake (≥40g/d for 10 years), family history of glaucoma, history of hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg) and/or history of intake of antihypertensive medication[13], diabetes(glycosylated haemoglobin ≥ 6.5% and /or anti-diabetic treatment[14], systemic corticosteroid intake (≥ 3 months) and history of Thyroid Disease was taken. Detailed clinical examination of the eyes including visual acuity using Snellen's / Landolt's Broken ring Chart, fundus examination by +90D lens and indirect ophthalmoscopy was done. Other ocular examination like IOP measurement (by Applanation tonometer), examination of angle of anterior chamber (by Slit Lamp Gonioscopy) and visual field charting (by Humphrey Field Analyser). General evaluation included anthropometric measurements – height and weight (for BMI), blood pressure by sphygmomanometer, blood sugar estimation (Fasting & Post prandial) and thyroid function test.

RESULTS

134 cases of POAG (Group I) and 134 controls (Group II) were enrolled in the study. Maximum, number of cases were of age group 60-69 years (36.6%). The number of POAG cases increased with age from 40 to 69 years of age.The sex distribution was almost the same in both the groups, 66 (49.3%) males in group I and 60 (44.8%) in group II vide Table 1. Majority of patients of group I (n=119; 88.8%) had bilateral disease. Thus the total number of eyes with POAG studied is 253 eyes. Maximum subjects of group 1 were in pre-obese and obese group (64.9%) while in group II maximum subjects are in normal BMI group (54.5%). This difference between the two groups is statistically significant. The odds of POAG increased with increasing body weight category. In underweight and normal weight groups, odds of POAG were less than unity whereas in pre-obese and obese age groups the odds were above unity. The association between BMI and POAG was statistically significant ($p<0.001$) vide Table 2. Significantly higher proportion of group I (35.1%) as compared to group II (17.9%) had a positive history of tobacco intake ($p=0.001$). Statistically the odds ratio for history of chronic tobacco intake was 2.48 proving it as a risk factor. Majority of subjects irrespective of their group did not consume alcohol. Proportion of group II cases taking alcohol (11.2%) was more as compared to that of group I (9.7%) ($p=0.690$). 25.4% of group I and 7.5% of group II had a positive family history of POAG. The difference in association of family history between the two groups was statistically significant. Also the odds ratio for family history was quite high (4.22) indicating it as a risk factor. Hypertension was seen in 35.1% of group I and 17.2% of group II. Hypertensives had 2.61 times higher odds in group I as compared to the other group which was statistically significant ($p<0.001$) suggesting it as a risk factor. The number of diabetics was more in group I (22.4%) as compared to group II (12.7%) and this difference was also significant ($p=0.037$). The odds ratio for history of diabetes was 1.99 suggesting it a possible risk factor. In group I, 2.2% of individuals had history of long term systemic steroid intake (>3 months) while in group II only 0.7% of individuals had the same history. This difference between the two groups was statistically insignificant (vide Table 3).

DISCUSSION

Glaucoma is a disease entity in the disease control strategy of the VISION 2020 initiative. It is the second leading cause of irreversible blindness in the adult population in India[8,15]. The rates of bilaterally blind because of POAG in the APEDS[16], ACES[17], CGS (Rural)[18], CGS (Urban)[10] and WBGS[19] were 11.1%, 1.6%, 3.2%, 1.5% and 5.2% respectively[20]. Risk for blindness from Primary Open Angle Glaucoma is high because of advanced stage at the time of diagnosis, onset of glaucoma at young age, inadequate intraocular pressure control, high rate of progression despite treatment, undiagnosed glaucoma and missed opportunities for diagnosing glaucoma[21]. Age is also a risk factor for the conversion from ocular hypertension to open-angle glaucoma[22] as has also been found in the present study where number of cases increased with advancing age. It appears that low-level axonal loss may occur with aging in healthy individuals, but it is unclear how this relates to glaucomatous optic nerve damage[21, 23,24]. The sex distribution was almost the same in both the groups, 66 (49.3%) males in group I and 60 (44.8%) in group II. These observations were similar to findings of Anhchuong Le *et al.* (2003)[12] and Palimkar A *et al.* (2001)[4]. On the contrary Naila Ali *et al.* (2007)[25] had reported that males are more prone to glaucomatous optic neuropathy, but overall the gender does not seem to have any significant influence on causation or occurrence of POAG. Whether a gender difference exists in the prevalence of POAG has been controversial. Numerous studies have reported that the prevalence of POAG is higher in men, others have reported a higher prevalence in women, and yet others have reported no gender difference in prevalence[26]. Majority of patients of group I (n=119; 88.8%) had bilateral disease. This finding was in concordance with the literature that Primary open-angle glaucoma is generally a bilateral disease of adult onset[8] though the presentation may be asymmetric so that one eye may have moderate or advanced damage, whereas the fellow eye may have minimal or no detectable damage[8].

The association between BMI and POAG was statistically significant ($p<0.001$), which is in concordance with observations made in other studies who also have documented a positive association between BMI and IOP[27, 28]. Thus obesity was proven as a risk factor for POAG. On the contrary Wishal D. Ramdas *et al.* (2011)[29], in a population-based Rotterdam study observed that obesity appears to be associated with a higher intraocular pressure and not open angle glaucoma in women. Pasquale LR *et al.* (2010)[30] reports that there is no significant relationship between cumulatively averaged body mass index (BMI) and POAG overall while Louis R. *et al.*[31] and Gasser P *et al.*[32] had shown that there may be an inverse association between BMI and POAG. Significantly higher proportion of group I (35.1%) as compared to group II (17.9%) had a positive history of tobacco intake ($p=0.001$). The finding clearly suggests that chronic tobacco intake was a risk factor for POAG. Recently in a cohort of African-American women, Wise L.A. *et al.* (2011)[33] have reported that smoking might be associated with increased risk of early-onset POAG. Kang, J.H. *et al.* (2011)[34] also reported cigarette smoking conferring risk to POAG. Similar findings were also reported by Bonovas *et al.* (2004)[35] and S.M. Chiotoroiu *et al.* (2013)[36]. Smoking as a risk factor is not supported by Degui Wang *et al.*(2012)[37]. Tobacco smoking causes a transient rise in the IOP. Immediately after smoking IOP rises possibly through a mechanism of vasoconstriction and elevated episcleral venous pressure[38]. We found no association of alcohol consumption with POAG similar to the findings of Kang JH *et al.* 2007[39], Wishal D. Ramdas *et al.* (2011)[29], Klein BE *et al.*[40] and SM Chiotoroiu *et al.* (2013)[36]. The difference in association of family history between the two groups (I & II) is statistically significant concluding a known family history as a risk factor for POAG. This result is in concordance with both Baltimore study[41], Blue mountain study[42] and supported by Chang TC *et al.* (2005)[43] and Sung VC, *et al.* (2006)[44]. One might well expect family history of POAG to be protective against late presentation because of increased awareness of the condition in the family members[41,42].

Significantly higher proportion of group I cases had hypertension as compared to group II ($p<0.001$). Hypertensives had 2.61 times higher odds of POAG as compared to normotensives. The findings of the present study are suggestive that hypertension is a risk factor for POAG. Blue Mountain study[45] too has shown significant association of hypertension with POAG and M J S Langman *et al.* (2005)[46] had opined that diagnosis of Glaucoma was more likely to be made in patients with hypertension. Blood pressure variable

related to glaucoma appears to be diastolic ocular perfusion pressure or the difference between diastolic arterial pressure and IOP[21]. However, on the contrary Bonomi L *et al.* (2000)[47] are of opinion that POAG is more prevalent among those with lower perfusion pressures. Again the number of diabetics is more in group I cases (22.4%) as compared to group II (12.7%) and this difference was statistically significant proving diabetes as a risk factor for POAG. Pasquale LR *et al.*[48] too have reported a positive association between Type 2 Diabetes Mellitus and POAG. The observation of our study is further supported by various studies like AGIS (Advanced Glaucoma Intervention Study)[49], CIGTS (Collaborative Initial Glaucoma Treatment Study)[50] and Los Angeles Latino Eye Study[51]. The Beaver Dam Eye Study, which found an incidence of 7.8% of POAG in diabetics compared with 3.9% in those without diabetes (P=0.0005), concluded that the presence of open angle glaucoma is increased in people with older-onset diabetes[52]. Diabetes is known to cause microvascular damage and may affect vascular autoregulation of the retina and optic nerve[51]. Evidence demonstrates that vascular disturbances to the the optic nerve's anterior portion are responsible for optic nerve head changes, which can result in glaucomatous optic neuropathy[51]. All these systemic factors could influence local IOP by affecting episcleral venous pressure, which regulates aqueous humor outflow across the trabecular meshwork into Schlemm's canal[38]. 2.2% of group I and 0.7% of group II individuals had history of long term systemic steroid intake (>3 months) but no significant association of use of systemic steroids was seen with occurrence of POAG. Bui *et al.* [53] showed that discontinuing nasal steroids might lower IOP in eyes with glaucoma, suggesting that nasal steroids might contribute to IOP increase. Yet Garbe *et al.*[54] reported that only patients receiving high doses of inhaled or nasal steroids for 3 or more months were at increased risk for Primary Open-angle glaucoma. Systemic steroids exert their influence on ocular pressure in sensitive individuals mainly by an increased inflow[55].

In group I, 11.2% of individuals had history of thyroid disease while in group II only 6.7% of individuals had the similar history. Although the odds of POAG were higher among those with thyroid disorder as compared to those not having thyroid disorder yet the association was not significant statistically (OR=1.75; p=0.199). J M Cross *et al.*[56] have reported that the prevalence of self reported glaucoma was significantly higher among those who had a history of thyroid problems compared to those who did not (6.5% vs. 4.4%, respectively; p=.0003). While George Kitsos *et al.* (2010)[57] and Motsko *et al.*(2008)[58] had demonstrated no association between hypothyroidism and POAG. Girkin and colleagues[59] in 2004 demonstrated that there was a significantly greater risk of subjects with a pre-existing diagnosis of hypothyroidism developing glaucoma. In severe cases of thyroid-associated ophthalmopathy obstruction of venous flow through the orbit may increase the IOP. Thyroid dysfunctions have been attributed in more than one way for causing intraocular pressure changes. In Graves disease, IOP may be raised as a result of contraction of the extraocular muscles against intraorbital adhesions or orbital congestion due to increased tissue volumes[56]. In the case of hypothyroidism, excessive mucopolysaccharide accumulation within the trabecular meshwork acts like a surfactant, sticking together adjacent endothelial membranes, which increases IOP as well as aqueous outflow resistance[56].

TABLE 1
Age and Sex Distribution

AGE	Group I (POAG CASES) Number (%) (n=134)	Group II (CONTROL GROUP) Number (%) (n=134)
40-49 yrs	26(19.4)	27(20.1)
50-59 yrs	35(26.1)	34(25.4)
60-69 yrs	49(36.6)	48(35.8)
70-79 yrs	20(14.9)	21(15.7)
≥ 80yrs	4(3)	3(2.2)
Sex		
MALE	66(49.3)	60(44.8)
FEMALE	68(50.7)	74(55.2)

TABLE 2
OBESITY (BMI) AS A RISK FACTOR FOR POAG

BMI	POAG Cases (n=134)		Control (n=134)		Significance of difference		
	No.	%	No.	%	χ^2	P	OR
Underweight (<18.5)	9	6.7	10	7.5	0.057	0.812	0.89 (0.35-2.27)
Normal (18.5–24.99)	38	28.4	73	54.5	18.84	<0.001	0.33 (0.20-0.55)
Pre-Obese (25–29.99)	71	53.0	44	32.8	11.10	0.001	2.31 (1.41-3.78)
Obese (>30)	16	11.9	7	5.2	3.85	0.050	2.46 (0.98-6.19)

χ^2=20.9 (df=3); p=0.321
(BMI Grades: ®K. Park;Park's textbook of Preventive and Social Medicine; 22nd edition; page 369.)

TABLE 3
PROBABLE RISK FACTORS IN PRIMARY OPEN ANGLE GLAUCOMA

Risk Factors	POAG Cases		Control		Statistical significance
	Number (n=134)	Percentage	Number (n=134)	Percentage	
Tobacco intake					
No	87	64.9	110	82.1	*χ^2=10.136 (df=1); p=0.001*
Yes	47	35.1	24	17.9	*OR=2.48 (95% CI:1.41-4.36)*
Alcohol intake					
No	121	90.3	119	88.8	*χ^2=0.160 (df=1); p=0.690*
Yes	13	9.7	15	11.2	*OR=0.85 (95% CI:0.39-1.87)*
Family history					
No	100	74.6	124	92.5	*χ^2=15.66 (df=1); p<0.001*
Yes	34	25.4	10	7.5	*OR=4.22 (95% CI:1.99-8.95)*
Hypertension					
No	87	64.9	111	82.8	*χ^2=11.14 (df=1); p<0.001*
Yes	47	35.1	23	17.2	*OR=2.61 (95% CI:1.47-4.62)*
Diabetes					
No	104	77.6	117	87.3	*χ^2=4.36 (df=1); p=0.037*
Yes	30	22.4	17	12.7	*OR=1.99 (95% CI:1.04-3.81)*
Steroid use					
No	131	97.8	133	99.3	*χ^2=1.02 (df=1); p=0.314*
Yes	3	2.2	1	0.7	*OR=3.0 (95% CI:0.31-29.7)*
Thyroid dysfunction					
No	119	88.8	125	93.3	*χ^2=1.648 (df=1);p=0.199*
Yes	15	11.2	9	6.7	*OR=1.75 (95% CI:0.74-4.15)*

CONCLUSION

Higher BMI, chronic tobacco intake, known family history, Hypertension and Diabetes were proved as risk factors for POAG. Advancing age was a probable risk factor for POAG. Thyroid dysfunction, Alcohol intake and Chronic Systemic Steroid intake though was more common in POAG cases but the comparision was statistically insignificant and hence cannot be taken as risk factors for POAG with surety. Therefore we feel that identification of the risk factors for POAG at the earliest is not only important from the public health view , but also for the doctor, as more the disease is progressed, more difficult it is to control and treat. For an individual, knowing the risks for POAG can influence his behaviours; it also affects the decision-making by the health care professional and the compliance and follow up by the patient. It is required by the health professionals to incorporate health programmes in their public awareness programmes to make people aware of the risk factors of this blinding disease and thus help themselves in preventing it.

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