

PRIMARY OPEN ANGLE GLAUCOMA IN THYROID DISORDER

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ABSTRACT

PURPOSE

To assess the association of thyroid profile with open angle glaucoma.

DESIGN

Cross-sectional observational study.

MATERIAL AND METHOD

128 cases of diagnosed thyroid disorder were enrolled. 5 cases dropped out. Ocular examination included applanation tonometry, stereoscopic optic disc photography, and automated perimetry. Correlative association of thyroid disorder and open angle glaucoma was assessed.

RESULTS

Of 123 patients of thyroid disorder, 87.8% had hypothyroidism and remaining 12.2% had hyperthyroidism. 15.74% of hypothyroidism and 20% of hyperthyroidism patients had open angle glaucoma, which was statistically significant (Pearson chi-square: Value=6.548, df=2, p=0.040). On multivariate analysis with other risk factors like female sex, family history of glaucoma, myopia, hypertension, and diabetes; it was found that hypothyroidism is an independent risk factor for open angle glaucoma.

CONCLUSION

All patients having thyroid disorder should be investigated for early diagnosis of open angle glaucoma so that if need be anti-glaucoma treatment is started at the earliest and the eye maybe saved from any further deterioration.

KEYWORDS

Open angle glaucoma, Hypothyroidism, Hyperthyroidism.

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INTRODUCTION: Glaucoma is an important cause of blindness worldwide as a rise in intraocular pressure is associated with optic disc damage. 1.5% of all individuals worldwide are affected by this disease.¹ Glaucoma is correlated with various systemic disorders,² like diabetes mellitus, hypertension, thyroid disorders. 42 million people in India are estimated to have thyroid disorder.³ The thyroid gland, under hypothalamic pituitary control, secretes 93% thyroxine (T4) and 7% triiodothyronine (T3). These hormones increase transcription of several genes known to affect catabolism. Iodine deficiency is the most common cause of hypothyroidism worldwide, but in iodine-sufficient regions, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (After thyroid surgery or antithyroid drug treatment) are more frequent.

Hyperthyroidism can be caused by abnormal thyroid stimulation (Graves' disease), intrinsic thyroid autonomy (Hyperfunctioning adenoma, toxic multinodular goiter), or excess thyroid stimulating hormone. Eye involvement in thyroid disease ranges from well-documented thyroid-associated orbitopathy to hypothyroid eye changes including conjunctival and periorbital oedema, blepharoptosis, and nyctalopia.⁴ Thyroid associated orbitopathy is an autoimmune disorder, which represents the commonest and most important extrathyroidal manifestation of Graves' disease. It may occur in patients without current or prior hyperthyroidism (Euthyroid or ophthalmic Graves' disease) or patients who are hypothyroid due to chronic autoimmune (Hashimoto's) thyroiditis.

Women are affected 2.5-6 times more frequently than men. Most patients affected are aged between 30-50 years.⁵

Although, a well-described association exists between Open-Angle Glaucoma (OAG) and thyroid-related orbitopathy. The possible relationship between OAG and either hypothyroidism or hyperthyroidism has been studied

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by many authors, but there is wide variation in the result outcome.

The reason for hypothyroidism causing rise in IOP was postulated by Smith et al. He reported that deposition of hyaluronic acid and related material in the trabecular meshwork of the eye causes rise in IOP.⁶ While in Grave's disease with thyroid associated orbitopathy, the pressure of the enlarged extraocular muscles against orbital adhesions might increase IOP. In addition, any increase in the volume of orbital contents might cause orbital congestion and this orbital congestion might also increase the episcleral venous pressure leading to glaucoma. Thyroid disorders induce heavy metabolic and enzymatic damage to cell function including increased levels of blood lipid profiles in hypothyroidism, decreased levels of blood lipid profiles in hyperthyroidism, accumulation of mucopolysaccharides in subcutaneous tissues in hypothyroidism, alterations in skin components, and body fluid distributions and disturbances in serum enzyme concentrations. In addition, associated immune disorders in some thyroid diseases increase thyroid stimulating or suppressing antibodies, which leads to other clinical manifestations.⁷⁻⁹ However, the impact of hypothyroidism on IOP in the setting of orbitopathy has not been clearly established. And thus, the association between hypothyroidism and glaucoma remains a hypothetical link, which needs further study. Keeping this in mind, we aimed to examine OAG and its association with thyroid disorder.

MATERIAL AND METHODS: It is a cross-sectional observational study conducted at Era's Lucknow Medical College and Hospital, Lucknow, India. 128 cases of diagnosed thyroid disorder were enrolled. 2 patients refused to participate, 3 patients did not turn up for detailed examination for detection of glaucoma. So, 123 cases were evaluated after clearance from institutional ethical committee and after the informed written consent. History in regard to thyroid status (Type, duration, and treatment status); history of any ocular complaints especially in reference to POAG symptoms were noted. Ocular examination including Intraocular Pressure (IOP) measurement by Goldmann applanation tonometry, gonioscopy by Goldman 3 mirror gonioscope for angle evaluation, dilated stereoscopic 30° colour retinal and optic disc photographs were taken using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany). Optic disc photographs were graded by one of two masked graders using a modified protocol.¹⁰ for measurement of optic disc dimensions. The camera magnification was corrected using the spherical equivalent refraction of each eye.

Screening automated perimetry (Humphrey 76-point suprathereshold test; Allergan Humphrey, San Leandro, CA, USA) was performed in all the subjects. The minimum diagnostic criteria for OAG were an abnormal Humphrey 30-2 Glaucoma Hemifield Test plus one or more of the following field defects not explained by ocular or neurologic causes: arcuate or paracentral scotoma, nasal step or advanced glaucomatous field loss. OAG was diagnosed when typical glaucomatous visual field loss on the

Humphrey 30-2 tests matched optic disc rim loss on the stereophotographs after excluding angle closure, rubeosis, or secondary glaucoma other than pseudoexfoliation.

Glaucoma cases were defined on basis of IOP >21 mmHg and with optic nerve head changes and/or visual field changes. Ocular Hypertension (OH) was diagnosed in subjects without characteristic glaucomatous disc or field changes, or secondary glaucoma, but with IOP >21mmHg.¹⁰ A detailed medical and family history was taken including a history of glaucoma in first-degree relatives. Systemic hypertension was defined as systolic blood pressure greater than 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg and/or history of intake of antihypertensive medication.¹¹ Diabetes was defined on basis glycated haemoglobin (HbA1c) and on antidiabetic treatment. HbA1c >6.5% is taken as the cut off value.¹² Myopia was defined as spherical equivalent refractive error -1.00 dioptre or greater. History of thyroid disease was ascertained including its aetiology and the age and thyroid status at diagnosis (Regardless of age, sex, duration, and treatment status of thyroid disorder with consent for inclusion in study).

Participants were grouped into hypothyroid cases and hyperthyroid cases on basis of history, examination, and thyroid function tests. Those with TSH level higher than 4.5 uU/mL were considered to have hypothyroidism and those with T₄ more than 12.5 uU/dL, T₃ level higher than 220 mg/dL, TSH lower than 0.1 uU/mL were considered as hyperthyroid subjects.

Data Analysis: All statistical analyses including logistic regression analyses were performed using Statistical Analysis System. In multiple logistic regression models, potential confounders included were age (Continuously), gender, family history of glaucoma, diabetes, hypertension, and myopia. P-values <0.05 were considered statistically significant.

RESULTS: Of 123 patients of thyroid disorder, 87.8% (108) had hypothyroidism and remaining 12.2% (15) had hyperthyroidism and all the more it was more prominent among females compared to males (Pearson chi-square: Value = 3.98, df=1, p=0.046). Females 87.8% (108) were affected more significantly than males (Female:Male=7:1). Mean duration of thyroid disorder was 4.138 years with SD 2.08 and mean age was 40.85 yrs. (Range is 16 to 70 years) with standard deviation (S.D.) of 11.047 yrs. 15.74% (17 of 108) of hypothyroidism and 20% (3 of 15) of hyperthyroid patients had open angle glaucoma, which was statistically significant (Pearson chi-square: Value=6.548, df=2, p=0.040).

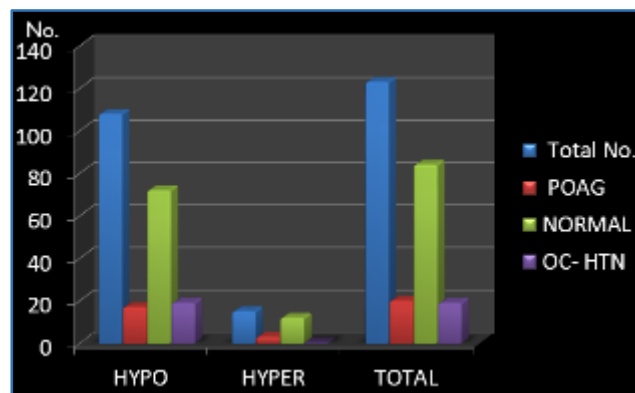
Of hypothyroidism patients, 17.59% (19 of 108) patients were found to have ocular hypertension with IOP >21 mmHg and no optic disc or visual field changes though none of the hyperthyroidism patients had ocular hypertension (Fig.1). On multivariate analysis with other risk factors like female sex, family history of glaucoma, myopia, hypertension, and diabetes, it was found that

hypothyroidism is independently a risk factor for open angle glaucoma. Logistic regression model of analysis showed that Thyroid, Female Sex, Upper Age and Present Family History (B values 1.753, 1.171, 0.042, 1.271) were independent risk factors in descending order for development of glaucoma while myopia, hypertension, and diabetes were not independently responsible for development of POAG.(Table 2).

Age: 40.05±11.047 (Range 16 to 70 years)
 Duration of thyroid disease = 4.138±2.08 years

Thyroid Status		Hypothyroid		Hyperthyroid		Chi-Sq., p-value
		N	%	N	%	
Sex	Male	2	13.33	43	39.81	3.98, 0.046
	Female	13	86.67	65	60.19	
Total		15	12.00	108	87.80	70.32, <0.0001

Table 1



Distribution of IOP in hypothyroidism and hyperthyroidism POAG significant in hypothyroidism (Pearson chi-square = 6.548; df=2; p=0.040).

Variable	Factor	Beta Co-Efficient	Standard Error	Significance	Exp (B)/Odds Ratio
Age	Age	0.042	0.021	0.034	1.043
Sex	Female	1.171	0.582	0.024	3.225
	Male	Ref.			
Thyroid	Present	1.753	0.697	0.012	5.775
	Absent	Ref.			
Family History of Glaucoma	Present	1.277	0.719	0.044	3.587
	Absent	Ref.			
Myopia	Present	1.501	1.281	0.241	4.487
	Absent	Ref.			
Hypertension	Present	-1.229	0.812	0.130	0.292
	Absent	Ref.			
Diabetes Mellitus	Present	-0.439	0.75	0.559	0.645
	Absent	Ref.			
Constant		-6.681	2.15	0.002	0.001

Table 2: (Risk Factors for POAG-Logistic Regression Model)

Note: According to logistic regression model, the significant risk factors for POAG are Upper Age, Males, Thyroid, and Present Family History.

DISCUSSION: Hypothyroidism is found to be more prevalent than hyperthyroidism as stated by Unnikrishan and Menon.³ and the same is supported by our study also. In women, the prevalence of hypothyroidism is higher as compared to men (11.4% in women as compared to 6.2% in men) in the study done by Unnikrishan and Menon in 2011. 7 in our study also women comprise 87.80% of the study group in comparison to 12.20% of men involved. There was no significant age related increase in the prevalence of reported thyroid disease. The mean age was 40.85 yrs. with standard deviation (S.D.) of 11.047 yrs. Mean age of development of POAG in hypothyroidism was 46.9 yrs. while it was 41.1 yrs. in hyperthyroidism as studied by AJ Lee et al.⁴ In hypothyroidism, the mechanism of open angle glaucoma is described as either the excessive mucopolysaccharide accumulation within the

trabecular meshwork acting as a surfactant or there is accumulation of hyaluronic acid in the trabecular meshwork and/or aqueous humour causing obstruction to drainage.^{3,13,14}

In hyperthyroidism, contracture of extraocular muscles against intraorbital adhesions or orbital congestion due to increased tissue volume is found to increase episcleral venous pressure leading to rise in intraocular pressure.^{15,16} In the literature, there is controversy regarding the association of thyroid disorder and POAG. Cheng and Perkins (1967).¹⁷ found 2% hypothyroidism patients having glaucoma. Another author, Safran AB (1997).¹⁸ evaluated intraocular pressure in thyroid disorder patients and found an increased risk of IOP rise in hypothyroid patients. Smith et al (1993).⁶ studied risk factors in POAG patients and found 23.4% POAG patients had hypothyroidism. Girkin and colleagues.¹⁹ in 2004 demonstrated that there was a significantly greater risk of developing glaucoma in subjects with a pre-existing diagnosis of hypothyroidism as compared with normal controls in a large male population

(OR, 1.40; 95% confidence interval, 1.01-1.97), from the Veterans Affairs Medical Centre in Birmingham, Alabama. Lin HC et al²⁰ conducted a 5 yrs. Population-based followup study (2010) and found that open angle glaucoma developed in 7.4% of patients with hypothyroidism.

Many other authors (Munoz-Negrete in 2000.²¹ Karadim in 2001.²² Motsko in 2008.²³ George Kitsos in 2010.²⁴) found no association of thyroid dysfunction and OAG. In our study, 16.26% cases had OAG. On further analysis, 15.74% (17 of 108 cases) of hypothyroidism and 20% (3 of 15 cases) of hyperthyroidism patients had open angle glaucoma, which was statistically significant (Pearson chi-square: Value=6.548, df=2, p=0.040) (Fig:4). The higher prevalence of OAG in our study could be because most of the patients included in the study were taking treatment for thyroid disorder and also were in the age group when the chances of development of glaucoma was highest. The association between current thyroxine use and OAG could be interpreted in at least two ways: (1) Current thyroxine use could be regarded as a surrogate for hypothyroidism. Reduced T3 and T4 levels prior to or during treatment could lead to various effects including increased mucopolysaccharide production, altered myocilin gene regulation or possibly morphogenetic effects on the optic nerve or (2) thyroxine treatment could have direct toxic effects on ocular structures.⁴

Of 108 cases of hypothyroidism, 17.59% (19 of 108 cases) had ocular hypertension with IOP >21 mmHg with no optic disc or visual field changes and thus not having absolute diagnosis of open angle glaucoma. These cases were asked to be under followup as they might develop open angle glaucoma in later stages. In a study done by Centanni and colleagues.¹⁴, IOP was increased even in subclinical hypothyroid patients. The theory proposed for borderline association between glaucoma and any reported thyroid disease is autoimmune mechanism in glaucoma development. Autoimmunity may also be linked with glaucoma pathogenesis.^{25,26} It is speculated that an autoimmune response to a sensitizing antigen may inflict damage to retinal ganglion cells or to the optic nerve vasculature. Autoimmune-mediated glaucoma injury may be more frequent in subjects in whom IOP has never been found to be elevated and could represent an autoimmune neuropathy. To support this theory, serum antibody titres should have been done, which is lacking in our study.

The association found between glaucoma and hyperthyroidism could relate to well-documented thyroid-associated orbitopathy. Proposed causes of glaucoma in hyperthyroid subjects include extraocular muscle contraction against orbital adhesions,¹⁵ trabecular meshwork, mucopolysaccharide deposition, direct thyrotoxic effects, a genetically-linked predisposition^{27,17} optic nerve head ischaemia, or decreased resistance to IOP.²⁸ Thyroid-associated orbitopathy in Grave's disease can increase IOP by blocking episcleral aqueous outflow.²⁸ Logistic regression model of analysis in our study showed that thyroid disorder (Especially hypothyroidism), age, female, sex, and family history (Wald statistics - 6.336,

4.045, 3.883, 3.157 respectively) were independent risk factors in descending order for development of glaucoma while association of myopia, hypertension, and diabetes was not significant independently.

There is not much evidence available right now regarding the screening of glaucoma patients for thyroid status and thyroid patients for development of glaucoma. Our study shows statistically significant association of thyroid disorder especially hypothyroidism with open angle glaucoma, although further evaluation is still warranted due to small sample size in our study.

LIMITATION OF STUDY: This study was performed in a resource poor setting where facility of optical coherence tomography was not available hence this early diagnostic tool for POAG could not be applied, but the HFA was used and its diagnostic utility was found in this study in thyroid disorder patients who were having mean duration of illness of less than five years.

CONCLUSION: The study revealed statistically significant higher incidence of POAG in thyroid disorders when compared to normal population. Thus, to conclude, all patients having thyroid disorder should be investigated for early detection of POAG, so that, if need be, antiglaucoma treatment is started early and eye is saved from going blind.

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