Prevalence of Open-angle Glaucoma, Glaucoma Suspect, and Ocular Hypertension in Thyroid-related Immune Orbitopathy

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Purpose: To determine the prevalence of open-angle glaucoma (OAG), glaucoma suspects (GS), and ocular hypertension (OHT) in patients with *thyroid-related immune orbitopathy* (TRIO) and compare it with a control group.

Patients and Methods: In this cross-sectional analytic study, 233 eyes of 117 patients with TRIO (case group) and 240 eyes of 120 normal age and sex-matched individuals (control group) underwent complete ocular examinations. Grave orbitopathy (GO) was diagnosed by clinical examinations with the help of an endocrinologist and para clinic tests. Controls were selected among apparently healthy individuals with no history of previous orbitopathy or thyroid diseases.

Results: Prevalence of OAG and OHT was 2.5% and 8.5% in the case group, respectively. In contrast, OAG was detected in only 2 eyes (0.8%) of the control group and there were no instances of GS or OHT in the control group. Although the prevalence of OAG and GS were higher in cases than controls, this difference was not statistically significant. However, OHT was more common in cases ($P < 0.01$). Ten eyes in the case group (4.3%) developed compressive optic neuropathy (CON); high intraocular pressure was detected in 5 of them (2.1%). All cases of OAG and GS in the case group were classified as stage 3 or higher of No symptoms or signs, Only signs no symptoms, Soft tissue, Proptosis, Extraocular muscle, Cornea, Sight loss. Active GO was only more prevalent in patients with OHT ($P < 0.001$).

Conclusions: The prevalence of OHT was higher in cases with GO than age and sex-matched controls. Ophthalmologic examinations including intraocular pressure measurement (and if needed automated visual fields) should be regularly performed in patients with GO particularly in higher stages and those with active disease.

Key Words: thyroid-related immune orbitopathy, ocular hypertension, glaucoma suspect, open-angle glaucoma

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Grave orbitopathy (GO) is the most common cause of bilateral and unilateral proptosis in adults. Both the orbitopathy and the functional disorder of the thyroid gland are probably secondary to an underlying immune dysfunction. The clinical signs and symptoms of GO may develop and progress independent of manifestations of the thyroid dysfunction and treatment of the hormonal abnormalities may have no impact on the course of the orbitopathy.[1–3]

Wessely first reported raised intraocular pressure (IOP) in GO in 1918.[4] However, IOP was normal in cases with hyperthyroidism in some earlier studies.[5] Factors which may lead to raised IOP consists of increased muscle, adipose and connective tissue volume, mucopolysaccharide precipitation in the trabecular meshwork, and blood stagnation secondary to increased episcleral venous pressure (EVP) in the limited intraorbital space.[6–8]

The prevalence of open-angle glaucoma (OAG) in patients with GO varies from 0.8% to 13.5% in different studies.[3,9,10] This variability may be due to diversity in interval between orbital involvement and diagnosis of glaucoma that may take several years. The prevalence of glaucoma is reported to be greater in patients with GO than the general population[9] but not all studies have confirmed this finding.[3,10]

This study was carried out to determine the prevalence of OAG, glaucoma suspects (GS) and ocular hypertension (OHT) in patients with GO referred to an endocrinology clinic to compare it with an age and sex-matched control group with no definite history of orbitopathy and/or thyroid disease.

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PATIENTS AND METHODS

Patients who had clinically diagnosed as GO were selected by convenient sequential sampling of new referrals to a private endocrinology clinic from February 2001 to February 2002, or by recalling documented definite cases by reviewing patients' records.

The entire project was totally approved by the Institutional Review Board of the Ophthalmic Research Center of Shaheed Beheshti University of Medical Sciences and all the cases and controls signed the informed consent for thorough physical and ocular examinations.

Inclusion criteria for the study were consistent with GO grading according to the No symptoms or signs, Only signs no symptoms, Soft tissue, Proptosis, Extraocular muscle, Cornea, Sight loss (NOSPECS) classification (Table 1) with lid retraction and lid lag with or without thyroid hormone dysfunction, which was detected by clinical examinations and para clinic tests for thyroid gland function. The diagnosis of GO was confirmed by an expert oculoplastic specialist.

In cases with no lid retraction, lid lag in the presence of other ocular signs of GO and no clinical and para clinical thyroid dysfunction, other causes of the ocular manifestations were excluded by relevant clinical examinations and imaging including orbital computed tomography (CT) scan and/or magnetic resonance imaging. All thyroid gland examinations and hormonal tests were performed and reviewed by an endocrinology specialist. Detailed ophthalmic examinations and tests were performed by a single glaucoma-expertise ophthalmologist.

The control group was selected from apparently healthy individuals who were companions of patients referred to an academic clinic for general problems after matching for age and sex. Inclusion criteria for the control group were lack of any previous or concurrent thyroid disease or orbitopathy confirmed physical examinations and ancillary tests described for the case group.

Exclusion criteria included any ocular disorder precluding fundus examination and history of orbital decompression surgery. GO was defined as active if clinical manifestations progressed or regressed with or without treatment during a 3-month period; and "inactive" when no change was observed during a comparable period regardless of sequels of GO.[11]

Collected data consisted of patients' age, sex, current thyroid function according to the clinical examinations and laboratory tests, signs, symptoms, and duration of orbitopathy, history and duration of systemic steroid therapy. Ocular examinations included best-corrected visual acuity evaluated by objective and subjective refraction and keratometry, relative afferent pupillary defect and color saturation tests (for asymmetric cases), ocular motility, slit lamp examination of anterior segment and anterior chamber angle examination with the help of Goldmann 3-mirror, and fundus examination with a +90 lens. Proptosis was measured with the Hertel exophthalmometer and IOP measurements in primary gaze by Goldmann applanation tonometer in the morning and evening. In the case of IOP, >21 mm Hg at any time (morning or evening), the measurement was repeated the next day at the same time and by the same person; cases with raised IOP in 2 subsequent measurements were considered as "elevated IOP."

TABLE 1. Different Stages of GO According to NOSPECS

Group	Description
N (0)	No symptoms
O (1)	Only signs, no symptoms: upper lid retraction and staring with or without upper lid lag or proptosis
S (2)	Soft tissue: tearing, foreign body sensation, retrobulbar problems, or photophobia and clinical signs including conjunctival and eyelid edema, conjunctival and episcleral vessels congestion, palpable lacrimal glands, orbital fat prolaps, palpable and edematous external ocular muscles beneath the eyelids
P (3)	Proptosis (together with signs or symptoms of soft tissue involvement)
E (4)	The involvement of external ocular muscles restricting ocular movements
C (5)	Corneal involvement
S (6)	Sight loss (compressive optic neuropathy)

In case of use of antiglaucoma medications, a washout period of 3 days for pilocarpine and 21 days for β-blockers and 48 hours for carbonic anhydrase inhibitors was considered to recheck the IOP.[4] Medications were restarted in patients with high IOP after washout period and confirmation of rised IOP.

Standard achromatic automated visual fields were obtained (Humphrey perimetry, 30-2 SITA standard strategy) in case of high IOP, detection of optic nerve pathology, decreased best corrected visual acuity and positive relative afferent pupillary defect or abnormalities of color saturation test.

According to the probability plot, visual fields were considered abnormal if 2 or more adjacent points were depressed ≥ 5 dB or 1 point was ≥ 10 dB depressed compared with surrounding points in any region of the central 30 degrees of the visual field, with mean deviation greater than 2 dB, pattern standard deviation outside the 95% confidence interval and glaucoma hemi-field test result out of normal range. If the first visual field was abnormal, the test would be repeated at least twice and then every 2 months. Visual fields were evaluated by examining probability plots, global indices, glaucoma hemi-field test, and the collaborative initial glaucoma treatment study system[12] by a glaucoma specialist.

Glaucomatous changes in the optic nerve were defined as cup disc ratio greater than 0.6, vertical cup asymmetry more than 0.2, neuroretinal rim loss or notching with or without a disc hemorrhages and nerve fiber layer defects.

Open angle glaucoma (OAG) was defined as glaucomatous changes in the optic nerve with corresponding visual field defects and high or normal IOP in the presence of an open angle (grade II or more according

to Shaffer's classification).[4] OHT was applied to cases with IOP $\geq$ 21 mm Hg, no glaucomatous changes in the optic nerve, normal visual fields, and an open angle. Due to limited follow-up period, glaucoma suspect was defined as normal IOP together with glaucomatous optic nerve changes but normal visual fields and an open angle.

Axial and coronal orbital CT scans and magnetic resonance imaging were performed in cases with clinical optic nerve dysfunction or abnormal findings in the optic nerve. Compressive optic neuropathy (CON) secondary to GO was considered if extraocular muscle index was more than 67% on coronal sections at a definite distance between the orbital apex and posterior aspect of the globe.[13,14]

All enrolled subjects underwent the above-mentioned systemic and ophthalmologic examinations at least every 2 months and followed for at least 4 months. The χ^2 and Fisher exact tests were applied for analysis of qualitative data and *t* test and analysis of variance tests were employed for quantitative data.

RESULTS

Out of 560 patients with Grave disease, 117 cases (81 female subjects, 69.2%) with graves orbitopathy (233 eyes; 1 patient was monocular) were enrolled in this study. The control group included 240 eyes of 120 persons (78 female subjects, 65%).

Mean age was 39.9 ± 13.4 (14 to 74 y) and 39 ± 14.2 (15 to 71 y) in cases and controls, respectively. Positive history of glaucoma in close relatives was not significantly different in cases (4.3%) and (6.7%) controls.

The prevalence of OAG was not significantly different in the 2 groups but the summation of prevalence of OAG and GS together was higher in cases (4.7%) than controls (0.8%) ($P < 0.02$) Table 2. Similarly, the prevalence of eyes with IOP $\geq$ 21 mm Hg was significantly higher in cases (13.3%) than controls (0.8%) ($P < 0.001$). All 6 eyes with OAG were at phase 3 of the NOSPECS classification, 3 out of 5 eyes, considered as GS, were at phase 3 and 2 eyes at phase 4. No positive family history of glaucoma was present in subjects with GS and OAG in both groups.

In the case group 115 (98.3%) were hyperthyroid according to the thyroid function tests at the time of diagnosis of Graves orbithopathy. However, only 6 (5.1%) had increased serum thyroid hormones at the time of ocular examinations Table 3.

TABLE 2. Frequency of Final Diagnosis Regarding Ocular Diagnosis in Both Groups

	Group	
Diagnosis	**GO No (%)**	**Control No (%)**
OAG	6 (2.6)	2 (0.8)
OHT	20 (8.6)*	0
GS	5 (2.1)	0
CON	5 (2.1)	0
Normal	197 (84.6)	288 (99.2)
Total	233 (100)	240 (100)

*Five eyes had OHT and CON simultaneously.

TABLE 3. Prevalence of Thyroid Function Status in 117 Patients With GO According to Time of Detection of Orbitopathy and Time of Ocular Examinations

	Time	
Thyroid function	**On Diagnosis of GO**	**On Ocular Examinations**
Hyperthyroidism	115 (98.3%)	6 (5.1%)
Hypothyroidism	0	4 (3.4%)
Subclinical hypothyroidism	0	3 (2.6%)
Euthyroid	2 (1.7%)	104 (88.9%)
Total	117 (100%)	117 (100%)

Exophthalmometric values for cases and controls were > 20 mm in 77% of cases and < 20 mm in 94% of controls ($P = 0.001$) Table 4.

Ten eyes (4.3%) in the case group developed changes in optic nerve as follows: disc hyperemia and swelling in 3 eyes, pallor and regional optic nerve atrophy in 3 eyes, and diffuse pallor and atrophy in 4 eyes. These eyes developed visual field changes as well, including generalized decreased sensitivity and blind spot enlargement in 3 eyes, and arcuate scotoma in 1 eye. All these 10 eyes were diagnosed as CON on orbital CT scan. These (4.3%) were classified as grade 6 of NOSPECS. IOP was high (> 21 mm Hg) in 5 of them.

Three eyes (1.3%) in the case group developed nonglaucomatous optic nerve and visual field changes including lower altitudinal scotomata in 2 eyes and diffuse decreased sensitivity in 1 eye with normal IOP. There was no sign of CON on CT scan. Two of them were classified as grade 2 and 1 as grade 3. No lesion was detected on brain CT scan and they were considered as ischemic optic neuropathy (ION).

Because of low number of samples and high standard deviation of the mean of duration of thyroid-related immune orbitopathy (TRIO) no significant relationship could be demonstrated between the duration of GO and OHT, GS, and OAG (Table 5).

Systemic steroids were prescribed for 26 patients (22%) to control active GO. The prevalence of high IOP was 23% in patients who used steroids and 11% in patients with no history of steroid use; statistically, this difference was not significant ($P = 0.08$) Table 6.

TABLE 4. Prevalence of Different Amounts of Exophthalmometry in Case and Control Groups

	Group	
Exophthalmometry	**Case Group**	**Control Group**
10-14 mm	2 (1)	81 (34)
15-19 mm	5 (22)	14 (60)
20-24 mm	145 (62)	14 (6)
25-30 mm	35 (15)	0

TABLE 5. The Duration of GO in Cases of OHT, GS, and OAG in Case Group

	Duration of Diseases (mo)		
Diagnosis (No. Eyes)	Mean ± SD	Minimum	Maximum
OHT (20)	79.5 ± 71	10	252
GS (5)	125 ± 96	23	240
OAG (6)	86.8 ± 140	84	240

The prevalence of *active* GO in eyes with OHT was higher than eyes with normal IOP ($P < 0.001$), but no significant difference was observed in eyes with OAG or GS and eyes with normal IOP regarding to the status of disease activity (Table 7).

DISCUSSION

The current study revealed an overall prevalence of high IOP in 11% of patients with GO including OAG 2.5% and OHT 8.5%.

The prevalence of OAG in eyes with GO and that of the control group was not significantly different.

Ohtsuka and Nakamura[9] studied 208 eyes of 104 patients with GO and reported that the prevalence of OAG and OHT was 6.5% and 22%, respectively, which was significantly higher compared with the normal Japanese population (1.4%). Despite a similar distribution of age and sex in this study (compared with ours), the higher prevalence of OHT and OAG could be due to patient selection; in the current study patients with GO were selected from a nonophthalmic center, (endocrinology clinic) which could be a better representative of the patient population, as opposed to a sample of cases at an ophthalmic referral center. On the other hand, because relaxation and anterior septal displacement of the orbit may play an important role in reducing intraorbital pressure[11,15] the different reported rates could be due to racial differences in orbital anatomy and connections of the eyelids to the anterior orbital wall.

In a retrospective study from Netherlands,[10] OHT and OAG were reported in 4.8% and 0.8% of patients with GO, respectively. Although the prevalence of OHT was higher than the general population (1.6%), the prevalence of OAG was almost the same.[10]

In a retrospective study on 500 patients with GO by Cockerham et al[3] from the United States, the prevalence of OHT was 24%. After exclusion of cases with established glaucoma before the development of orbitopathy and follow-up of cases with OHT, the prevalence of OAG was 2%.[3] In the Cockerham[3] study neither family history of OAG nor systemic steroid use was correlated with OAG and GS which is also compatible with our findings.

TABLE 6. The Frequency of Systemic Steroid Use Regarding High IOP in 233 Eyes in Case Group

History of Steroid Use	Positive	Negative	Total
IOP $\geq$ 21 mm Hg	11 (23)	20 (11)	31
IOP $<$ 21 mm Hg	40 (77)	162 (89)	202
Total	52 (100)	182 (100)	233

Our findings indicate that although active GO was associated with OHT, no such relationship was observed with OAG and GS. As mentioned, with acute rise of EVP, IOP may be increased by a one-to-one ratio (1 mm Hg increase of EVP yields in 1 mm Hg rise in IOP) but the relation is more complex in chronic cases.[6] Therefore, ocular hypertension may be expected with active orbitopathy, however, with disease progression, other manifestations may be seen. Persistent IOP rise may be associated with progression of glaucomatous neuropathy and the pathologic process may be halted with remission of the orbitopathy or decrease in IOP. Nevertheless, our study indicated that IOP may remain elevated despite disease remission. It may be presumed that chronic and persistent EVP elevations because secondary changes in these structures or that the aqueous drainage system becomes compromised.

CON due to active GO, may show various manifestations such as optic nerve head swelling and hyperemia, diffuse or localized pallor, increased cupping, or even a normal appearing nerve associated with decreased visual acuity and visual field defects despite normal IOP. CON has been observed in 5% of cases with GO in different studies[16,17] and its prevalence was 4.3% in this series.

A recent study[6] evaluated the change in IOP in subjects with GO after orbital decompression, strabismus surgery, and orbital radiation and concluded that orbital decompression and strabismus surgery resulted in a significant reduction in IOP in the early postoperative period, especially in subjects with preoperative IOP greater than 21 mm Hg. There was no statistically significant reduction in IOP after orbital radiation.

We observed some cases of regional or diffuse optic nerve head atrophy with normal IOP and no glaucomatous optic nerve changes accompanied by visual field defects. In these cases no underlying pathology, intracranial problem, or systemic disorders except for systemic hypertension and diabetes mellitus were detected. Because no compression was seen on the optic nerve on orbital CT scan, these cases were diagnosed as ION. In the Ohtsuka study, similar cases were reported to have normal tension glaucoma with a prevalence of 6.5%.[9] One case of ION was reported in the Cockerham study.[3] However, an ischemic process caused by fibrous tissue formation and traction leading to microvascular disorders may be present in GO, which may lead to an ischemic neuropathy. Further studies are needed to clarify such a possibility. Recently, He et al[18] reported that the incidence of OHT in TRIO was 31.3% and was more prevalent in men than women. This incidence is much higher than our study. The difference may be due to earlier diagnosis and management that may control the IOP in our setting.

In conclusion, the prevalence of OHT in patients with GO is higher than the normal population. However,

TABLE 7. Prevalence of OHT, GS, OAG, and Normal IOP in 233 Eyes in Case Group, Regarding the Status of TRIO (Disease Activity)

	Diagnosis				
GO	**OHT No (%)**	**GS No (%)**	**OAG No (%)**	**Normal IOP***	**Total**
Active	16 (80)	4 (80)	2 (33)	85 (42)	107
Inactive	4 (20)	1 (20)	4 (67)	117 (58)	126
Total	20 (100)	5 (100)	6 (100)	202 (100)	233

*IOP less than 21 mm Hg was considered as normal.

the results of this study strongly recommend routine ophthalmic examinations and automated perimetry particularly in higher stages and during active phases of disease. Because the effect of moderate rises of IOP may take several years to cause glaucomatous optic atrophy and associated visual field scotomata to full-fit the diagnosis of glaucoma, applying modern devices may be helpful for diagnosis of at risk patients in an earlier stage.

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