Prevalence and Severity of Ophthalmic Manifestations of Graves’ Disease in Mashhad University Endocrine Clinics

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Abstract

Purpose: To evaluate the prevalence and severity of ophthalmic manifestations of Graves’ disease in the Mashhad University of Medical Sciences endocrine clinics.

Methods: In a multicenter prospective descriptive study, patients with Graves’ disease that were being followed in Mashhad University of Medical Sciences endocrine clinics were recruited for the study, from December 2002 to September 2005. A comprehensive ophthalmic assessment including visual acuity, external eye examination, ocular motility examination, exophthalmometry, tear status evaluation, intraocular pressure (IOP) measurement, slit lamp examination, and funduscopy were performed. We also evaluated the recent thyroid disease status and the treatment regimen of all patients. The classification of ophthalmopathy was based on the classification by the American Thyroid Association.

Results: Sixty-eight patients (24 men and 44 women) were studied. The mean age of the patients was 37.98±14 (range 15 to 71) years. The mean duration of systemic thyroid disease was 2.46±2.36 years (range 6 months to 11 years). The majority of patients had hyperthyroidism at the time of visit (86.2%) and only 3% of the patients were hypothyroid. The most common complaints of patients were foreign body sensation (54%) and puffy eyelids (48.4%). Mean Snellen visual acuity was 0.9±0.17. The most prevalent sign was increased IOP in upgaze (88.2%). Increased IOP in upgaze had a statistically significant association with limitation of extraocular movements (4.57 mm Hg vs. 2.56 mm Hg in the presence and absence of gaze limitation, respectively; P=0.03). The most common clinically evident abnormality was lid retraction, which was noticed in 64.2% of patients. Lid retraction was bilateral in 95.3% of the cases. Exophthalmos was present in 53%. Injection over the insertion of horizontal recti was noticed in 48.5% and ocular motility limitation in 19.1%. Tear breakup time was abnormal (less than 10 seconds) in 55.9% of the patients; with a mean of 17.76±6.18 mm (range 4-30 mm); the Schirmer’s test was abnormal in 10.3% of patients too. The patients had a mean modified Werner’s NOSPECS classification score of 3 with an SD of 1.46. The score was significantly affected by sex, and was higher in males (3.58 vs. 2.63 in females; P<0.01). The score was positively correlated with the age of the patients (r=0.298, P=0.016).

Conclusion: Our study of a relatively large number of patients replicated the known epidemiological facts regarding Graves’ ophthalmopathy in Mashhad with slight epidemiologic variations.

Keywords: Grave’s Disease, Hyperthyroidism, Thyroid-associated Ophthalmopathy, Grave’s Ophthalmopathy, Thyroid Related Immune Orbitopathy

Introduction

Graves’ ophthalmopathy (GO) is a chronic, debilitating infiltrative eye and orbital disease that is often associated with Graves’ disease. About 50% of patients with Graves’ disease will develop GO and severe forms affecting 3% to 5% of patients. The onset of the ophthalmopathy is in most cases concomitant with the onset of hyperthyroidism, but eye disease may precede or follow hyperthyroidism.1

GO affects females six times more than males (86% versus 14% of cases, respectively). The female-to-male ratio is reduced to 4:1, in severe forms of the eye disease.2

The male to female ratio of patients with systemic hyperthyroidism is 4:1, whereas the male to female ratio for patients with ophthalmopathy is 2.5:1.4.5

The age-adjusted incidence rate was 16 cases per 100,000 population per year for females and 2.9 cases per 100,000 populations per year for males. The peak incidence rates were bimodal, occurring in age groups 40 to 44 and 60 to 64 years in females and 45 to 49 years and 65 to 69 years in males.3

The ocular changes associated with thyroid dysfunction have been recognized for more than 150 years, yet controversy still remains regarding the pathogenesis, pathophysiology, and management of this disease.4-6

The following treatment modalities are available in patients with severe GO: systemic corticosteroids given orally or parenterally, retrobulbar irradiation (high-voltage orbital irradiation), microsurgical orbital liposuction, surgical orbital decompression, immunosuppressive agents such as cyclosporine, plasmapheresis, IV gamma globulins, or a combination of these therapeutic options.

There are few studies to evaluate the prevalence and severity of GO in Iranian patients.11 In our study, we aimed to investigate the prevalence and severity of ophthalmopathy in Graves’ patients in our area (north-east of Iran). We therefore examined a large number of patients with Graves’ disease for the prevalence of GO, as well as the influence of various factors such as age, gender, and thyroid status in severity of ophthalmopathy. In addition, we compared and contrasted the clinical presentations in Iranian patients with those of previously reported studies.

Methods

This was a multi-centric, cross-sectional descriptive study between December 2002 and September 2005. All patients with confirmed diagnosis of Graves' disease in the endocrine clinics of the Mashhad University of Medical Sciences who have any signs or symptoms of GO were recruited to the study. The diagnosis of Graves’ disease was based on clinical and laboratory findings of diffuse enlargement of thyroid gland, triiodothyronine, thyroxin, T3 resin uptake, raised free T4 or T3 levels, and suppressed thyroid stimulating hormone levels.

Information regarding age, occupation, family history, ocular symptoms, and associated systemic disease was also obtained. The records of patients were reviewed to evaluate the recent thyroid disease status and the treatment regimen.

The comprehensive ophthalmic examination was performed in a standardized way for all patients. Best corrected visual acuity (BCVA) was documented by Snellen chart. Visual field test requested in any case suspicious to optic nerve dysfunction.

Intraocular pressure (IOP) was measured in primary position and upward gaze with applanation tonometer. Eyelid, conjunctiva and ocular motility status were assessed. Limitation of ocular motility evaluated qualitatively in horizontal and vertical fields of vision and scored from -1 to -4.

Tear status was evaluated with Schirmer's test and tear breakup time (TBUT). We considered Schirmer's test less than 10 mm and TBUT less than 10 seconds as tear film dysfunction. Retraction of either upper or lower eyelid was defined by any exposed superior or inferior sclera beyond the limbus in the primary gaze. Degree of proptosis was measured by the Hertel exophthalmometer. Proptosis was defined as the measurement of protrusion of the globe >20 mm from the lateral orbital rim in either eye or any discrepancy in the degree of protrusion of the two eyes by >2 mm. Corneal involvement was assessed with fluorescein staining under slit lamp biomicroscopy. Fundus examination was...
done for evaluation of disc and retina. Also, computed tomography (CT) or magnetic resonance imaging (MRI) was taken when required.

The classification of GO was based on the classification by the American Thyroid Association from Werner’s [12] (Table 1). The relation of their thyroid functions and ocular manifestations were also evaluated.

Table 1. Modified Werner’s NOSPECS classification score.

<table>
<thead>
<tr>
<th>Score</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No signs or symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Only signs</td>
</tr>
<tr>
<td>2</td>
<td>Soft tissue involvement with symptoms and signs</td>
</tr>
<tr>
<td>3</td>
<td>Proptosis (≥ 20 mm)</td>
</tr>
<tr>
<td>4</td>
<td>Extraocular muscle involvement</td>
</tr>
<tr>
<td>5</td>
<td>Corneal involvement</td>
</tr>
<tr>
<td>6</td>
<td>Sight loss (visual acuity ≤ 0.67)</td>
</tr>
</tbody>
</table>

Results

Sixty-eight patients (24 men and 44 women) were studied during the study period from December 2002 to September 2005. The mean age of patients was 37.98±14 years (range 15 to 71 years). The mean duration of systemic thyroid disease was 2.46±2.36 years (range 6 months to 11 years). The majority of patients had hyperthyroidism at the time of visit (86.2%), only 3% of patients had a hypothyroid state and the remaining were euthyroid. While 76.7% of patients were receiving methimazole, 11.7% of patients were under treatment with levothyroxine. A history of radioactive iodine treatment was present in 23.3% of patients.

The most common complaint of the patients was foreign body sensation (54%) and puffy eyelids (48.4%) (Table 2). The mean Snellen visual acuity was 0.9±0.17 (8/10-10/10). The most prevalent sign (Figure 1) was increased intraocular pressure in upgaze (88.2%), which was clinically significant (≥5 mm Hg) in 13.2% of patients. The mean intraocular pressure in primary position was 15.90±3.56 mm Hg, which was increasing to 18.76±4.57 mm Hg in upgaze. The increment in intraocular pressure in upgaze was statistically significant (P<0.0001).

The most common apparent sign was lid retraction, which was noticed in 64.2% of patients. (Figure 1) Lid retraction was bilateral in 95.3% of cases. Exophthalmos was present in 53% of patients which was bilateral in the majority of cases (85.6%). Injection over the insertion of horizontal recti was noticed in 48.5% of patients, which was more prominent over the insertion of medial recti. Limited ocular movements were present in 19.1% of patients. Most of patients had limitation in upgaze and abduction (16.2%), and unexpectedly the down gaze was the least limited gaze (5.9%).

Increased intraocular pressure in upgaze had a statistically significant correlation with limitation of extraocular movements (4.57 mm Hg vs. 2.56 mm Hg in the presence and absence of gaze limitation, respectively; P=0.03). Also, clinically significant increase in intraocular pressure was more common in patients with limited gaze (P=0.01).

Tear break-up time (TBUT) had a mean of 11.61±3.46 seconds (range 4-20 seconds). It was abnormal in 55.9% (in 1.5% of patients were less than 5 seconds and between 5 to 10 seconds in 54.4% of patients) with a mean of 17.76±6.18 mm (range 4-30 mm), the Schirmer’s test was abnormal in 10.3% of patients.

The patients had a mean modified Werner’s NOSPECS classification score (Table 1) of 3 with a SD of 1.46 (Figure 2). The score was significantly affected by sex, and was higher in males (3.58 vs. 2.63 in male and female, respectively; P<0.01) (Figure 3). The score was positively correlated with the age of patient (r=0.298, P=0.016) (Figure 4). A correlation between the score and disease duration or TSH level could not be proven.

Table 2. Common complaints in thyroid-related immune orbitopathy

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign body sensation</td>
<td>54.0</td>
</tr>
<tr>
<td>Puffy lids</td>
<td>48.4</td>
</tr>
<tr>
<td>Pain</td>
<td>45.2</td>
</tr>
<tr>
<td>Tearing</td>
<td>40.3</td>
</tr>
<tr>
<td>Photophobia</td>
<td>35.5</td>
</tr>
<tr>
<td>Incomplete lid closure</td>
<td>32.3</td>
</tr>
<tr>
<td>Staring</td>
<td>31.7</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>29.0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>17.7</td>
</tr>
</tbody>
</table>
Figure 1. Common physical findings in thyroid related immune orbitopathy
**Figure 2.** NOSPECS classification. Modified Werner’s score of 2 and 3 were more frequent among our patients.

**Figure 3.** NOSPECS classification according to age. The score was positively correlated with the age of patient ($r=0.298$, $P=0.016$)

**Figure 4.** Bilateral upper and lower lid retraction and injection over medial rectus muscles.
Discussion

The epidemiologic characteristics and clinical course ophthalmopathy in Graves' disease has been the subject of many studies. Our study, conducted with a relatively large number of patients, gave the following epidemiological results.

In other studies female to male ratio were between 4 to 6:1, whereas in our patient sample GO affected females only two times more frequently than males (64% versus 36% of cases, respectively). On average, females were presented ten years earlier than males (The mean age for females was 34.77±13.34 and for males 44.73±13.42 years). GO was found to be more common among women. As many affected patients were middle-aged women, the importance of functional and cosmetic consequences should be considered in the context of early diagnosis and treatment.

The most common ocular signs among patients with thyroid ophthalmopathy in this study were increased intraocular pressure in upgaze (88.2%), lid retraction (64.2%), exophthalmos (53%) and periorbital swelling (50%). The rate of lid retraction in this study was lower than the rates reported by Bartley et al\textsuperscript{3} (90.0%), Vangheluwe et al\textsuperscript{15} (90.0%), and Teshome and Seyoum\textsuperscript{16} (83.8%).

Strabismus is common in GO and usually presents in hypotropic or esotropic forms. In this study, 13.3% of patients had strabismus, the majority of whom had hypotropia or esotropia.

The prevalence of restrictive myopathy in the studies by Vangheluwe et al\textsuperscript{15} and Bartley et al\textsuperscript{3} were 40% and 43%, respectively. In this study, the prevalence of EOM involvement with limited gaze was 19.1%, whereas frank strabismus noted only in 13.3%.

Optic neuropathy (ON) was found in one of our patients (Figure 5). This patient had the complete constellation of classic findings at the same time: eyelid retraction, exophthalmos, optic nerve dysfunction, extraocular muscle involvement, and hyperthyroidism. Visual impairment (visual acuity and visual field changes) was the main symptom of ON. However, other methods used to detect optic neuropathy are more sensitive than vision tests alone and also take into consideration in early forms of optic nerve damage.\textsuperscript{17} Using visual evoked cortical potentials (VECP) Salvi et al found signs indicative of optic neuropathy in 21 out of 88 patients (23.8%).\textsuperscript{18} Considering the high prevalence of optic neuropathy found by these authors, it is surprising that clinically significant optic neuropathy (with visual deterioration) was much fewer in our patients. However, the diagnosis of optic neuropathy in our patients was based on clinical examination visual deterioration and visual field defects only. More sensitive methods were not available. Therefore, in our study the actual occurrence of optic neuropathy is probably underestimated.

![Figure 5. A: a patient with bilateral eyelids retraction, proptosis, and restricted ocular motility. His best corrected visual acuity reduced to counting fingers at 4 meters due to optic neuropathy. B: Axial CT scan showing horizontal muscles enlargement and bilateral proptosis.](image-url)
GO is frequently associated with elevated intraocular pressure on upgaze. In this study, 88.2% of patients had abnormal intraocular pressure in upgaze which was greater than or equal to 5 mm Hg rise in 13.2%. This finding was similar to those of Gamblin and et al study. Increased intraocular pressure in upgaze had a significant correlation with limitation of extraocular movements (4.57 mm Hg vs. 2.56 mm Hg in the presence and absence of gaze limitation, respectively; P=0.03). However, the utility of IOP change on upgaze in clinical practice remains controversial. In Reader's study on 100 healthy eyes, the mean increase in IOP at 20 degree upgaze was 1.75 (SD 1.49) mm Hg. Five subjects had an increase in IOP of 4 mm Hg and one subject had a 6 mm Hg increase. Therefore, the pressure elevation has to be interpreted very carefully.

Similar to Perros and et al study, age and gender influence the severity of thyroid-associated ophthalmopathy. In our cases the score was significantly higher in males (3.58 vs. 2.63 in male and female, respectively; P<0.01). Also the score was positively correlated with the age of patients (r=0.298, P=0.016) (Figure 3). We also included the patients' smoking history in our study. The numbers of smokers in the current study were small such that a definitive conclusion regarding the relation of smoking and thyroid eye disease cannot be made from this study.

Marcocci et al showed that there is no clear relationship between the treatment of hyperthyroidism and the course of ophthalmopathy. Antithyroid drugs may improve oculomotor manifestations, whereas prescription of radioactive iodine and thyroidectomy cause worsening of ophthalmopathy. In our cases while 76.7% were receiving methimazole, 11.7% of our patients were under treatment with levothyroxine. A history of radioactive iodine treatment was present in 23.3% of the patients. The majority of the patients had hyperthyroidism at the time of visit (86.2%); only 3% of the patient had a hypothyroid state and others were euthyroid. The course of ophthalmopathy in our patients may be changed by these interventions.

**Conclusion**

Our study of a relatively large number of patient replicated the known epidemiological facts regarding GO in Mashhad. Our results corresponded with numerous other studies with slight epidemiologic variations. The prevalence of most of the ocular complications increased with increasing age. The incidence of higher severity score of ophthalmopathy was significantly more among older patients.

**Acknowledgment**

This study was supported by grant number 82061 awarded by the Research Committee of Mashhad University of Medical Sciences.

**References**