Clinical evaluation of Graves ophthalmopathy in north-east Islamic Republic of Iran

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التقييم السريري لاعتلال العين في داء غريفز في شمال شرق جمهورية إيران الإسلامية

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الخلاصة: تقيِّم هذه الدراسة معدل انتشار ووخامة التظاهرات العينية في داء غريفز لدى 68 مريضاً ممن راجعوا عيادات الغدد الصماء في جامعة مشهد للعلوم الطبية في المدة من كانون الأول/ديسمبر 2002 إلى أيلول/سبتمبر 2005. وقد كان العمر الوسطي للمرضى 38 عاماً (الانحراف المعياري: 14.0 عاماً والمجال: 15–71 عاماً). وكانت الشكوى الأكثر شيوعاً هي الإحساس بوجود جسم غريب (54.0%) وانتفاخ الأجفان (48.4%) أما الاضطراب الأكثر شيوعاً ووضوحاً فكان انكماش الجفن لدى 64.2% من المرضى (ثنائي الجانب في 95.3% منهم). وقد كان لدى المرضى درجات أحراز متوسطة وفق تصنيف ويرنر لاعتلال العين في داء غريفز (NOSPECS) وقد بلغت 3.00 (بانحراف معياري 1.46). وقد كانت الدرجات المحرزة لدى الذكور [3.58 (بانحراف معياري 1.44)] أعلى بشكل يعتد به إحصائياً مما هو عليه لدى الإناث [2.63 (بانحراف معياري مقداره 1.35)]، وكانت مترابطة ترابطاً إيجابياً مع العمر.

ABSTRACT This study evaluated the prevalence and severity of ophthalmic manifestations in all Graves disease patients (*n* = 68) presenting to endocrine clinics at Mashad University of Medical Sciences between December 2002 and September 2005. The mean age of patients was 38.0 (SD 14.0) years, range 15 to 71 years. The most common complaints were foreign body sensation (54.0%) and puffy eyelids (48.4%). The most common apparent abnormality was lid retraction in 64.2% of patients (bilateral in 95.3% of cases). The patients had a mean modified Werner's NO SPECS classification score of 3.00 (SD 1.46). The score was significantly higher in males than females [3.58 (SD 1.44) versus 2.63 (SD 1.35)] and was positively correlated with age.

Évaluation clinique de l'ophtalmopathie basedowienne dans le nord-est de la République islamique d'Iran

RÉSUMÉ Cette étude a évalué la prévalence et la gravité des manifestations ophtalmologiques chez les patients atteints de la maladie de Graves-Basedow (n = 68) qui se sont présentés au service de consultations externes d'endocrinologie de l'Université des Sciences médicales de Mashad entre décembre 2002 et septembre 2005. L'âge moyen de ces patients était de 38,0 (écart type 14,0) ans, avec des extrêmes de 15 et 71 ans. Les sujets se plaignaient le plus souvent de sensation de corps étranger (54,0 %) et de gonflement des paupières (48,4 %). L'anomalie apparente la plus courante était la rétraction palpébrale chez 64,2 % des patients (bilatérale dans 95,3 % des cas). Les patients avaient un score moyen de 3,00 selon la classification NOSPECS de Werner modifiée (écart type 1,46). Ce score était significativement plus élevé chez les hommes que chez les femmes (3,58 [écart type 1,44] contre 2,63 [écart type 1,35]) et positivement corrélé à l'âge.

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Introduction

The relationship between exophthalmos and thyroid disease was first recognized by the Iranian scientist Sayyid Ismail Al-Jurjani in the 12th century [*1,2*]. 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 affect 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 [*3*]. GO was found to affect females 6 times more frequently than males (86% versus 14% of cases, respectively), but the female:male ratio was reduced to 4:1 in severe forms of eye disease [*4*]. The age-adjusted incidence was 16 cases per 100 000 population per year for females and 2.9 cases per 100 000 population per year for males. The peak incidence rates were bimodal, occurring in age groups 40–44 years and 60–64 years in females and 45–49 years and 65–69 years in males [*5*].

The ocular changes associated with thyroid dysfunction have been recognized for many years, yet controversy remains regarding the pathogenesis, pathophysiology, and management of this disease [*6,7*]. Newer studies have brought possible significant insights to the understanding of the pathogenesis of GO. It has been found that thyroid-stimulating hormone (TSH)-receptors are also present in retrobulbar tissue [*8,9*], which is why it is suspected that TSH-receptor antibodies contribute to the development of GO by the stimulation of these retro-orbital tissue TSH-receptors.

General health-related quality of life is markedly impaired in patients with GO, and could be even worse than in patients with other chronic conditions such as diabetes, emphysema or heart failure [*10*]. In addition, severe forms of GO can lead to sight-threatening complications. Evaluation of the epide-miologic characteristics and severity of GO in each region can help to inform better decisions about increased quality of life and adequacy of education and counselling in patients with GO.

There have been few studies to evaluate the prevalence and severity of GO in Iranian patients [*11*]. Due to this lack of data, we aimed to investigate the prevalence and severity of ophthalmopathy in Graves patients in our area (north-east of the Islamic Republic 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, sex and thyroid status, on the severity of ophthalmopathy. In addition, the clinical presentation of our patients was compared and contrasted with that of previously reported studies.

Methods

This was a multi-centre, prospective, descriptive study between December 2002 and September 2005. All patients with confirmed diagnosis of Graves disease attending the endocrine clinics of the Mashad University of Medical Sciences during the study period were recruited to the study. The diagnosis of Graves disease was based on clinical and laboratory findings of diffuse enlargement of thyroid gland, free triiodothyronine (T_3) and thyroxine (T_4) levels, T_3 resin uptake, raised free T_4 or T_3 levels, suppressed TSH levels. The study had no exclusion criteria and all patients with documented history of hyperthyroidism with any age, onset or type of intervention were included.

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

A comprehensive ophthalmic examination was performed in a standardized way for all patients. Best corrected visual acuity was documented by Snellen chart. A visual field test was requested in any case suspected of optic nerve dysfunction.

Intraocular pressure (IOP) was measured by applanation tonometer in the primary position and with upward gaze. Eyelid, conjunctiva and ocular motility status were assessed. Tear status was evaluated with Shirmer test and tear break-up time. We considered Schirmer < 10 mm and tear break-up time < 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. The 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 2 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 Werner's classification, as endorsed by the American Thyroid Association [*12*] (Table 1). The relation of the thyroid functions and ocular manifestations were also evaluated.

Table 1 **Modified Werner's NO SPECS classification score**

Score	Sign
0	No signs or symptoms
1	Only signs
2	Soft tissue involvement with symptoms and signs
3	Proptosis (≥ 20 mm)
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loss (visual acuity ≤ 0.67)

Results

A total of 68 patients were studied during the period December 2002 to September 2005: 24 men (36%) and 43 women (64%) (data missing for 1 patient). The mean age of the patients was 38.0 [standard deviation (SD) 14.0] years (range 15 to 71 years). The mean age for females was 34.8 (SD 13.3) years and for males 44.3 (SD 13.4) years.

The mean duration of systemic thyroid disease was 2.5 (SD 2.4) years (range 6 months to 11 years). The majority of patients had hyperthyroidism at the initial presentation to the ophthalmologist (86.2%); only 3% of patients were hypothyroid and the remainder 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 presenting complaints of patients were foreign body sensation (54.0%) and puffy eyelids (48.4%). Ocular and periocular pain was the complaint in 45.2% of patients and the eyeball was the most prominent site of pain

in the majority (78.5%). Other symptoms included: tearing (40.3%), photophobia (35.5%), staring (31.7%), blurred vision (29.0%) and diplopia (17.7%).

Mean Snellen visual acuity was 0.90 (SD 0.17). The most prevalent sign was increased intraocular pressure on upgaze (88.2%), which was clinically significant (≥ 5 mmHg) in 13.2% of patients. The mean intraocular pressure in the primary position was 15.90 (SD 3.56) mmHg, which increased to 18.76 (SD 4.57) mmHg on upgaze. The increment in intraocular pressure on upgaze was statistically significant ($P < 0.0001$).

Figure 1 **Bilateral upper and lower lid retraction and injection over medial rectus muscles**

Table 2 **Common physical findings in thyroid related immunological orbitopathy in 68 patients with Graves disease**

Finding	%
IOP rise	88.2
Lid retraction	64.2
Periorbital swelling	50.0
Staring	48.6
Injection over horizontal recti insertion	48.5
Exophthalmos	53.0
Lagophthalmos	28.1
Punctate corneal epithelial erosion	25.0
Peripapillary venous tortuosity	20.9
Diffuse injection	20.9
Dry eye	20.6
Restricted eye movements	19.1
High IOP, upgaze	19.1
Eye deviation	13.3
Significant IOP rise	13.2
Caruncle swelling	7.4
High IOP, primary position	4.4
Decreased levator function	4.4
Chemosis	4.4
Disc swelling	1.5
Corneal ulcer	1.5
Corneal opacity	1.5
Relative afferent pupillary defect	0.0

IOP = intraocular pressure.

The most common apparent abnormality was lid retraction, which was noticed in 64.2% of patients (Table 2). Lid retraction was bilateral in 95.3% of cases. Exophthalmos was present in 53.0% of patients and 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 rectus (Figure 1). Limited ocular movements were present in 19.1% of patients. Most of the patients had limitation on upgaze and abduction (16.2%), and unexpectedly the downgaze was the least limited gaze (5.9%).

Tear break-up time had a mean of 11.61 (3.46) seconds (range 4–20 seconds). It was abnormal in 55.9% of patients (< 5 seconds in 1.5% and 5–10 seconds in 54.4% of patients). With a mean of 17.76 (SD 6.18) mm (range 4–30 mm), the Schirmer test was abnormal in 10.3% of patients. Increased IOP on upgaze had a statistically significant correlation with limitation of extraocular movements (4.57 mmHg versus 2.56 mmHg in the presence and absence of gaze limitation, respectively; $P = 0.03$). Also, a clinically significant increase in IOP

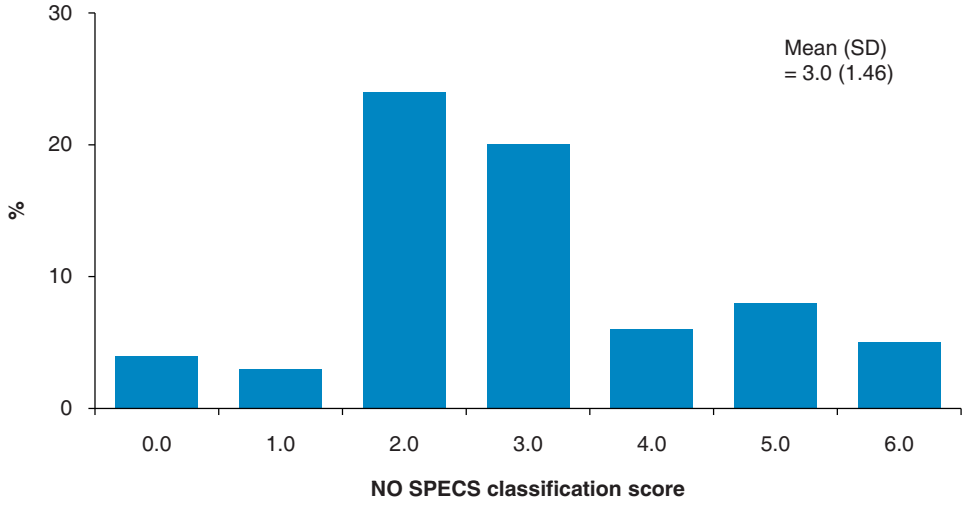


Figure 2 **Modified Werner's NO SPECS classification of 68 patients with Graves disease**

was more common in patients with limited gaze ($P = 0.01$).

The patients had a mean modified Werner's NO SPECS classification score of 3.00 (SD 1.46) (Figure 2). The mean score was significantly higher in males [3.58 (SD 1.44)] than females [2.63 (SD 1.35)] ($P < 0.01$). The score was positively correlated with the age of the patient ($r = 0.298$, $P = 0.016$) (Figure 3). A correlation between the score and disease duration or TSH level could not be shown.

Clinically detectable optic neuropathy was found in 1 of our patients (Figure 4). 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 optic neuropathy.

Discussion

Our study, conducted with a relatively large number of patients, can be compared with other similar studies. GO was found to be more common among women. However, in other studies the female:male ratio was between 4:1 and 6:1 [*5,13,14*], whereas in our sample it was less than 2:1 (64% of cases were females versus 36% males). On average, females presented 10 years earlier than males; the mean age of females in our study was 34.8 years and for males 44.3 years. As the majority of affected patients were middle-aged women, the importance of the functional and cosmetic consequences should be considered in the context of early diagnosis and treatment.

The most common complaints of our patients were foreign body sensation (54.0%) and puffy eyelids (48.4%), followed by ocular and periocular pain (45.2%), tearing

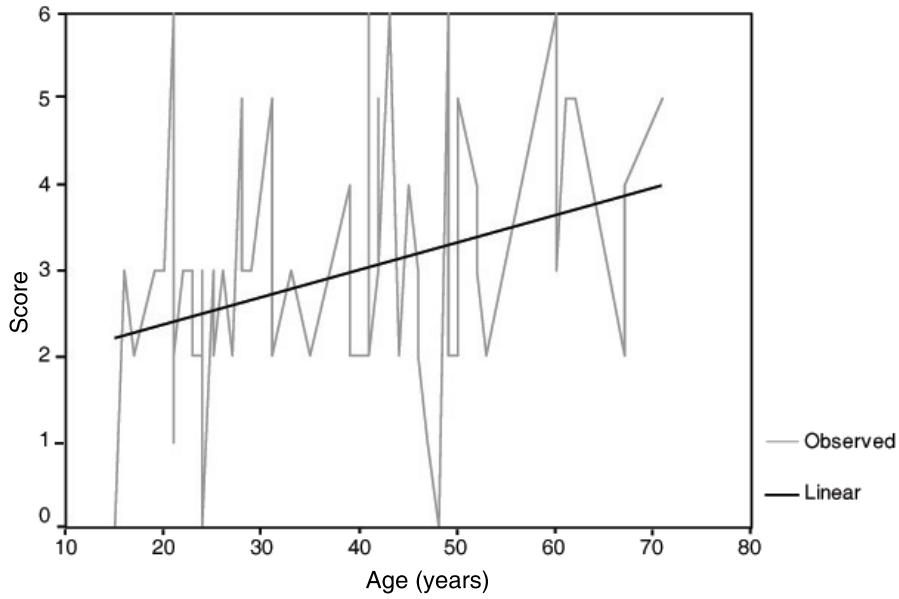


Figure 3 **Correlation of modified Werner's NO SPECS classification score and age in 68 patients with Graves disease (*r* = 0.298, *P* = 0.016)**

(40.3%), photophobia (35.5%), staring (31.7%), blurred vision (29.0%) and diplopia (17.7%).

The most common ocular signs among patients with thyroid ophthalmopathy in this study were increased IOP on upgaze (88.2%), lid retraction (64.2%), exophthalmos (53%) and periorbital swelling (50.0%). The rate of lid retraction in our study was lower than the rates reported by Bartley et al. [*5*] (90.0%), Vangheluwe et al. [*15*] (90.0%), and Teshome and Seyoum [*16*] (83.8%).

Strabismus is common in GO and usually presents in the hypotropic or esotropic forms. In our 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. [*15*] and Bartley et al. [*5*] were 40% and 43% respectively. In our study, the prevalence of extraocular muscle involvement with limited gaze was 19.1%, whereas frank strabismus was noted in only 13.3%.

Clinically detectable optic neuropathy was found in 1 of our patients. Visual impairment (visual acuity and visual field changes) was the main symptom. However, other methods used to detect optic neuropathy are more sensitive than vision tests alone and also take into consideration early forms of optic nerve damage [*17*]. Using visual evoked cortical potentials, Salvi et al. found signs indicative of optic

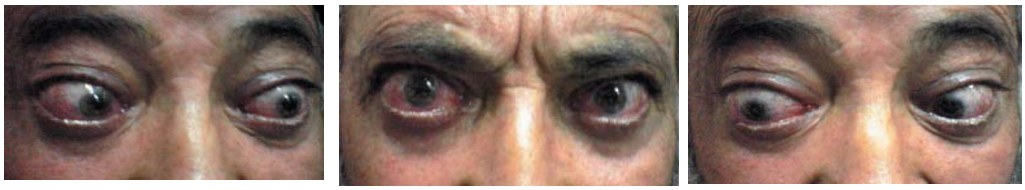
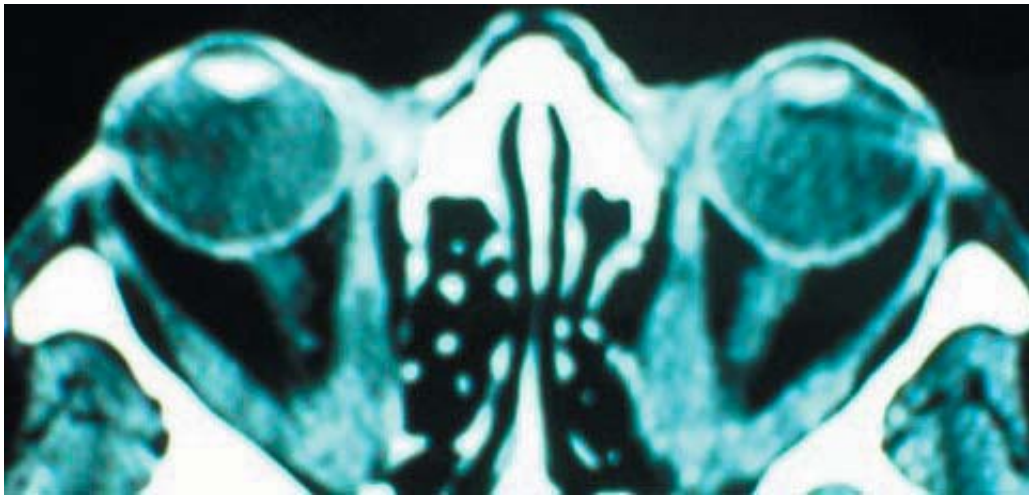


Figure 4
(a) Patient with bilateral lid retraction, proptosis, restricted ocular motility. His best corrected visual acuity reduced to 4 m finger-counting due to optic neuropathy (left: patient looking left; centre: patient looking straight; right: patient looking right)



(b) Axial CT scan showed horizontal muscles enlargement and bilateral proptosis

neuropathy in 21 out of 88 patients (23.8%) [*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 rarer in our patients. However, the diagnosis of optic neuropathy in our patients was by clinical examination only, based on visual deterioration and visual field defects. More sensitive methods were not available and therefore the actual occurrence of optic neuropathy is probably underestimated.

GO is frequently associated with elevated IOP on upgaze. In this study, 88.2% of patients had abnormal IOP on upgaze which was ≥ a 5 mmHg rise in 13.2%. This finding is similar to those of Gamblin et al. [*19*]. Increased IOP on upgaze had a significant correlation with limitation of extraocular movements (4.57 mmHg versus 2.56 mmHg in the presence and absence of gaze limitation respectively; $P = 0.03$).

However, the usefulness of measuring 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) mmHg [*20*]. A total of 5 patients had an increase in IOP of 4 mmHg and 1 patient had a 6 mmHg increase. Therefore, the pressure elevation has to be interpreted very carefully.

Similar to Perros et al.'s study [*13*], age and sex influenced the severity of thyroid-associated ophthalmopathy. In our cases the score was significantly higher in males than females (3.58 versus 2.63 respectively; $P < 0.01$) and was positively correlated with the patients' age ($r = 0.298$, $P = 0.016$). Although we included the patients' smoking history in our study, the number of smokers was small and a definitive conclusion regarding the relation between smoking and thyroid eye disease could not be made from this study.

Marcocci et al. showed no clear relationship between treatment of hyperthyroidism and the course of ophthalmopathy [*21*]. Antithyroid drugs may improve ocular manifestations, whereas prescription of radioactive iodine and thyroidectomy cause worsening of ophthalmopathy. In our cases while 76.7% 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 majority of patients had hyperthyroidism at the time of first presentation (86.2%), 3% of patients had a hypothyroidic state and the remainder were euthyroid. These interventions may change the course of ophthalmopathy in our patients.

Conclusion

The epidemiological characteristics and clinical course of ophthalmopathy in Graves disease has been the subject of many studies. Our study of a relatively large patient sample revealed the known epidemiological facts regarding Graves ophthalmopathy in north-east of Islamic Republic of Iran. Our results correspond with numerous other studies with slight epidemiological variations. The prevalence of most of the ocular complications increased with increasing age. The incidence of higher severity score of ophthalmopathy was significantly greater among older patients.

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