

ORIGINAL ARTICLE

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# Prevalence of Graves ophthalmopathy among patients with thyroid disease

## ABSTRACT

### Objective

This study determined the prevalence of Graves ophthalmopathy among thyroid-disease patients at a tertiary government hospital.

### Methods

Patients with thyroid disease seen at a tertiary hospital from February to September 2007 were enrolled. All patients underwent ophthalmologic examination consisting of visual-acuity testing; exophthalmometry; examination for presence of lid retraction, lid lag, and lateral flare; globe position; external-ocular-muscle-movement grading; corneal light reflex; and direct funduscopy examination.

All clinical findings were recorded and data were analyzed. Chi square and Fisher's exact tests determined the association of gender and age to the different ocular signs and symptoms. One-way analysis of variance (ANOVA) compared the average number of ocular symptoms among the different age groups.

### Results

A total of 121 patients, 20 males and 101 females, with thyroid disease were evaluated. 47.93% had Graves ophthalmopathy, occurring more frequently among patients aged between 30 and 49 years. The most common signs were eyelid retraction, proptosis, and lid lag.

### Conclusion

Graves ophthalmopathy occurs frequently among patients with thyroid disease, especially those more than 30 years of age.

**Keywords:** *Graves ophthalmopathy, Graves disease, Lid retraction, Lid lag, Proptosis, Thyroid disease*

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GRAVES disease usually occurs in conjunction with hyperthyroidism, and ophthalmopathy is most commonly observed among those with the active or treated form of the disease. It is also seen in Hashimoto's disease, carcinoma of the thyroid, or other forms of thyroid disease.<sup>1</sup> Patients with Graves disease may present with ophthalmological signs and symptoms, that can appear before other signs of hyperthyroidism or even after regression of the disease. Thus, ophthalmological signs can lead to a diagnosis of Graves disease.<sup>2</sup>

A recent epidemiological study of white American patients with Graves ophthalmopathy placed the overall age-adjusted incidence rate at 16 per 100,000 per year for women and 3 per 100,000 for men. It affected women approximately six times more frequently than men. The peak incidence rates occurred in the age groups 40 to 44 years and 60 to 64 years in women and 45 to 49 years and 65 to 69 years in men. The median age at the time of diagnosis was 43 years (range, 8 to 88 years).<sup>1</sup>

Graves ophthalmopathy appears to be an organ-specific autoimmune disorder. It is also known as thyroid eye disease or thyroid-associated ophthalmopathy. Progression of the disease usually stops on its own within a two-year period and it rarely recurs. Mild symptoms may completely self-resolve, but treatment may be necessary to restore eyelid function, improve appearance, and correct vision.<sup>3,4</sup>

This study determined the prevalence of Graves ophthalmopathy and its common ocular signs and symptoms among thyroid-disease patients in a tertiary hospital.

## METHODOLOGY

This study used a descriptive cross-sectional design. The study population consisted of 121 thyroid-disease patients seen at the thyroid clinic of Jose R. Reyes Memorial Medical Center from February to September 2007. The patients underwent complete ophthalmological examination, which included visual-acuity testing using the Jaeger's near chart; exophthalmometry using the Hertel exophthalmometer; examination of eyelid for presence of lid retraction, lid lag, and lateral flare; globe position (axial, medial, and lateral); external-ocular-muscle-movement grading; corneal light reflex; and direct funduscopic examination using ophthalmoscope to check the status of the optic nerve.

Patients at the thyroid clinic were diagnosed to have thyroid disease based on the following criteria: presence of goiter or enlargement of thyroid gland or presence of thyroid dysfunction based on laboratory tests.

Based on the American Academy of Ophthalmology guidelines, Graves ophthalmopathy is present if eyelid retraction occurs together with objective evidence of thyroid dysfunction, or exophthalmos, or optic-nerve dysfunction, or extraocular-muscle involvement. If eyelid

retraction is absent, then Graves ophthalmopathy may be diagnosed only if exophthalmos, optic-nerve involvement, or restrictive extraocular myopathy coexist with thyroid dysfunction and no other causes for the ophthalmic features are apparent.

All clinical findings and personal details were recorded in a specially designed form. Data were analyzed using Stata software. Chi-square and Fisher's exact tests were used to determine if gender and age were associated with the different symptoms. One-way analysis of variance (ANOVA) was used to compare the average number of ocular symptoms among the different age groups and Bonferroni's test was done for multiple comparisons.

## RESULTS

A total of 121 patients were included in this study, 20 (16.53%) males and 101 (83.47%) females. Most were 30 to 49 years old (64.46%). A total of 58 (47.93%) patients, 8 males and 50 females, had Graves ophthalmopathy. There were more patients with bilateral (65.5%) than unilateral (34.5%) ophthalmopathy. Age and gender were not significantly associated with ophthalmopathy (Table 1).

Among those with ophthalmopathy, the most common symptom was lid retraction (88%), followed by proptosis (76%), lid lag (69%), staring (66%), and periorbital edema (62%). No patient had optic neuritis (Table 2).

Age was significantly associated with most of the symptoms. There were more patients ( $p = 0.001$ ) below 50 years old with lid retraction than those 50 and above. Among the three age groups, 30 to 49 had the highest proportion of patients with proptosis, lid lag, staring, and periorbital edema. Conjunctivitis, chemosis, and lagophthalmos were highest among 50 years old and above. EOM palsy and strabismus were significantly more prevalent among 50 and above (Table 2). Gender was not associated with any of the symptoms of ophthalmopathy.

Among those with ophthalmopathy, the mean number of ocular symptoms of those < 30 years old were significantly lower ( $p = 0.0001$ ) than those 30 to 49 ( $p < 0.001$ ) and those 50 years old and above ( $p = 0.001$ ). On the other hand, the average number of ocular symptoms between males and females were not significantly different ( $p = 0.30$ ) from each other. The same pattern was seen among those with unilateral and bilateral ophthalmopathy. Among those with unilateral ophthalmopathy, those < 30 years old had significantly lower number of ocular symptoms compared to those 30 to 49 ( $p = 0.005$ ) (Table 3).

## DISCUSSION

The prevalence of Graves ophthalmopathy in this study was 47.93%, notably lower than that reported by Besharati and colleagues (60.0%),<sup>4</sup> Nordyke and associates (91.4%),<sup>5</sup> and Bartley et al. (90.0%).<sup>6</sup>

It is the most common cause of unilateral and bilateral proptosis in adults. Proptosis occurs because the orbital contents are confined within the bony orbit, and

decompression can only occur anteriorly.<sup>1-3, 7</sup> Besharati and colleagues found that bilateral ophthalmopathy occurred more frequently than unilateral ophthalmopathy and the frequency increased with age.<sup>4</sup> The eyes are usually involved asymmetrically and rarely involved unilaterally. For unilateral proptosis, assessment for retrobulbar tumor is, therefore, necessary.<sup>8</sup>

Table 1. Distribution of patients with thyroid ophthalmopathy by age group and gender.

Characteristic	Without Ophthalmopathy	With Ophthalmopathy		p <sup>a</sup>
		Unilateral	Bilateral	
Age group (years)				
<30 (n = 13)	7 (41.18)	3 (17.65)	7 (41.18)	0.23 <sup>b</sup>
30-49 (n = 78)	43 (55.13)	12 (15.38)	23 (29.49)	
50 & above (n = 26)	13 (50.00)	5 (19.23)	8 (30.77)	
Gender				
Male (n = 20)	12 (60.00)	4 (20.00)	4 (20.00)	0.48
Female (n = 101)	51 (50.50)	16 (15.84)	34 (33.66)	
Total (n = 121)	63 (52.07)	20 (16.53)	38 (31.40)	

<sup>a</sup>Chi-square test; <sup>b</sup>Ophthalmopathy categories used—with and without

Table 2. Distribution of signs and symptoms of ophthalmopathy by age group and gender.

Signs/Symptom	Percent	Age Group			p <sup>a</sup>	Gender		p <sup>a</sup>
		< 30	30 to 49	50 and above		Male	Female	
Lid retraction	87.93	10 (90.9)	31 (100)	10 (62.5)	0.001 <sup>b</sup>	6 (75.0)	45 (90.0)	0.25
Proptosis	75.86	4 (36.4)	29 (93.6)	11 (68.8)	0.001	5 (62.5)	39 (78.0)	0.39
Lid lag	68.97	3 (27.3)	28 (90.3)	9 (56.3)	<.001	5 (62.5)	35 (70.0)	0.69
Staring	65.52	2 (18.2)	27 (87.1)	9 (56.3)	<.001	5 (62.5)	33 (66.0)	1.00
Periorbital edema	62.07	2 (18.2)	23 (74.2)	11 (68.8)	0.004	6 (75.0)	30 (60.0)	0.70
Conjunctivitis	53.45	1 (9.1)	19 (61.3)	11 (68.8)	0.004	6 (75.0)	25 (50.0)	0.26
Chemosis	51.72	1 (9.1)	18 (58.1)	11 (68.8)	0.006	6 (75.0)	24 (48.0)	0.26
Lagophthalmos	44.83	1 (9.1)	15 (48.4)	10 (62.5)	0.020	5 (62.5)	21 (42.0)	0.45
Dry eye	43.10	0	15 (35.7)	10 (62.5)	0.066 <sup>b</sup>	5 (62.5)	20 (40.0)	0.27
EOM palsy	8.62	0	0	5 (31.3)	0.001 <sup>b</sup>	2 (25.0)	3 (6.0)	0.14
Strabismus	5.17	0	0	3 (18.8)	0.018 <sup>b</sup>	1 (12.5)	2 (4.0)	0.37
Ophthalmoplegia	3.45	0	0	2 (12.5)	0.073 <sup>b</sup>	1 (12.5)	1 (2.0)	0.26
Diplopia	3.45	0	0	2 (12.5)	0.073 <sup>b</sup>	1 (12.5)	1 (2.0)	0.26
Ptosis	1.72	0	0	1 (6.3)	0.276 <sup>b</sup>	1 (12.5)	0 (0.0)	0.14

<sup>a</sup>Chi-square test

<sup>b</sup>Fisher's exact test

Table 3. Mean number of ocular signs and symptoms among those with ophthalmopathy.

Characteristic	Unilateral	Bilateral	Total
Age group (years)			
< 30	1.33 ± 0.58	2.63 ± 1.85	2.27 ± 1.68
30 to 49	7.17 ± 2.12	6.21 ± 2.88	6.58 ± 2.62
50 and above	3.8 ± 3.56	7.82 ± 2.99	6.56 ± 3.61
p <sup>a</sup>	0.003 <sup>b</sup>	0.001 <sup>c</sup>	0.0001 <sup>d</sup>
Gender			
Male	6.00 ± 2.94	7.75 ± 4.99	6.88 ± 3.91
Female	5.31 ± 3.40	5.71 ± 3.02	5.58 ± 3.12
p <sup>e</sup>	0.72	0.24	0.30
Total	5.45 ± 3.25	5.92 ± 3.25	p = 0.60 <sup>e</sup>

<sup>a</sup>One-way analysis of variance (ANOVA)

<sup>b</sup>Bonferroni's test, < 30 was significantly lower than 30 to 49 (p = 0.005)

<sup>c</sup>Bonferroni's test, < 30 was significantly lower than 30 to 49 (p = 0.011) and 50 and above (p = 0.001)

<sup>d</sup>Bonferroni's test, < 30 was significantly lower than 30-49 (p < 0.001) and 50 and above (p = 0.001)

<sup>e</sup>Independent t-test

The occurrence of different signs and symptoms of ophthalmopathy in Graves disease has been the subject of many studies. In a study by Nordyke and colleagues, proptosis and lid retraction were the most important signs of the disease and proptosis mostly occurred in the 30- to 49-year age group.<sup>5</sup> It was similarly observed in a study done by Teshome and Seyoum.<sup>9</sup> In a clinical review by Carter,<sup>10</sup> ophthalmopathy was present in 2% to 7% of patients with Graves hyperthyroidism and the main manifestations were proptosis, ophthalmoplegia, and lid

retraction. Bartley<sup>8</sup> found a 2.2% decrease in visual acuity secondary to optic neuropathy and constant diplopia. Of one-third of patients with eye discomfort, the most common complaint was dry eye. They also showed that the ratio of women to men was 1:0.6 with a bimodal incidence in the 40- to 44-year and 60- to 64- year age groups. Approximately 90% of the patients had hyperthyroidism, 3% had Hashimoto's disease, and 5% had euthyroidism. Unilateral or bilateral lid lag was common and was noted in 50% of patients during the primary clinical examination.<sup>8</sup> At the time of diagnosis of Graves disease, the most common ophthalmological symptom was pain. Signs and symptoms that significantly changed between the first and the final visits included tearing, pain, ocular discomfort, photophobia, lid retraction, lid lag, conjunctival injection, chemosis, lid fullness, and exophthalmos.

Emergency conditions associated with Graves

ophthalmopathy included optic neuropathy, corneal ulceration, globe subluxation, and periorbital edema with chemosis.<sup>11</sup> Early diagnosis and treatment is important as there is a direct relationship between decreased vision and the effect of treatment.

Graves ophthalmopathy may appear before, during, or after systemic presentations of thyroid disease. In a study by Besharati and associates, the most common complaints at the time of referral were nonocular, although most cases of ophthalmopathy occurred during the first 18 months after diagnosis of Graves hyperthyroidism.<sup>4</sup> Marcocci et al. showed that there was no clear relationship between treatment of hyperthyroidism and the course of ophthalmopathy.<sup>12</sup> Antithyroid drugs may improve ocular manifestations, whereas prescription of radioactive iodine and thyroidectomy can cause worsening of ophthalmopathy.

Graves ophthalmopathy was associated with extensive ocular morbidity in more than 90% of patients with hyperthyroidism.<sup>13</sup> One of the most valuable diagnostic tests for ophthalmopathy is an orbital CT scan, in conjunction with a clinical examination and thyroid function tests. If Graves ophthalmopathy is clinically diagnosed, there was no need for further imaging; but if imaging is necessary, MRI is more sensitive than CT in showing compression of the optic nerve, although CT is sometimes required to visualize the orbital bony structures for optic-nerve decompression.<sup>14</sup>

Ampudia and coworkers investigated the occurrence of exophthalmos diagnosed by Hertel exophthalmometry and CT scan. Exophthalmos by Hertel exophthalmometry was measured as  $22.5 \pm 2.5$  mm for the right eye and  $23.2 \pm 3.2$  mm for the left eye. The measurements made by CT scan were smaller ( $20.8 \pm 3.2$  mm and  $20.9 \pm 2.9$  mm for the right and left eyes, respectively) but this difference was not statistically significant.<sup>15</sup> The study showed that the muscles were not equally involved and the medial recti muscles were most commonly involved.

Regulation of thyroid function did not always improve Graves ophthalmopathy and may worsen the condition in some euthyroid patients.<sup>16-17</sup> In patients with hyperthyroidism, ophthalmopathy usually occurred within 18 months of disease onset. Park et al. showed that Graves ophthalmopathy also affected the quality of life.<sup>13, 16, 18</sup>

In summary, Graves ophthalmopathy was clinically apparent in 58 out of 121 (47.93%) patients examined, 50 of whom were females. The highest overall prevalence was observed in those 30 to 49 years of age, and bilateral ophthalmopathy (65.5%) occurred more frequently. The most common symptoms were lid retraction, proptosis, lid lag, staring, and periorbital edema.

Ophthalmologic examination should be done routinely on patients with thyroid disease. Regular follow-up should include monitoring of thyroid exophthalmos by exophthalmometry. Imaging studies may be performed as needed to ascertain the status of the disease.

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