Proportion and Clinical Profile of Thyroid Ophthalmopathy in Patients with Graves' Disease Presenting at a Tertiary Care Centre in Kerala

Liya K.Y.[1], Naina Jabeen Hyder[2], Neeta Sidhan[3], Shaji Ankan[4]

[1, 2, 3] Department of Ophthalmology, Regional Institute of Ophthalmology Thiruvananthapuram, Kerala, India.
[4]Department of Ophthalmology, Government medical College, Konni, Kerala, India.

ABSTRACT

BACKGROUND

Thyroid eye disease is a relatively rare condition, with an incidence of 2.9 to 16.0 cases per 100 000 population per year. Approximately 50 % of patients with Graves' disease (GD) develop clinically apparent thyroid eye disease. It may cause severe damage to vision and orbital architecture. It is the most frequent cause of unilateral or bilateral proptosis in adults.

METHODS

A cross sectional study of 80 patients with GD was carried out in association with thyroid clinic of Government Medical college Thiruvananthapuram for a period of 1 year from April 2017 to March 2018. Subjects who have a prior diagnosis of Graves' disease including those who are on antithyroid drugs were included in the study. Patients who are sick due to other systemic diseases like cardiac failure and end stage renal disease were excluded.

RESULTS

Eighty patients with mean age of 45.31 years were studied. Out of them, 66% were females and 34% were males. Ophthalmopathy was present in 38.8%.Majority had mild and bilateral disease (61.2 %). Only a small percentage had sight threatening disease (6.4 %).The mean age of patients with ophthalmopathy was 47.93. Major population with ophthalmopathy was females. Majority of patients with ophthalmopathy (64.5 %) retained a good visual acuity better than 6 / 9. Lid retraction was the most common manifestation among patients with Graves' ophthalmopathy that is 74.2% followed by exophthalmos (64.5 %) and eye movement restriction and soft tissue involvement (58.1 %). Diplopia, optic nerve dysfunction were rare (3.2 %). Only 19.3 % patients had active disease according to clinical activity score. Major clinical sign of activity was redness of conjunctiva. Maximum no. of patients with active disease had a clinical activity score of 4. Smoking showed a significant association with the severity of ophthalmopathy. (p value 0.001) There was a significant association between age and activity of disease. (p value 0.021). No association was found between duration of disease with presence or severity of ophthalmopathy. There was no association between co- morbidities with presence or severity of ophthalmopathy. No association was found between hormone status and presence or severity of ophthalmopathy.

CONCLUSIONS

Our results indicated that the prevalence of ophthalmopathy in our population with GD evaluated at our tertiary care centre was similar to that reported in the Caucasians of European origin. Clinically active and sight threatening ophthalmopathy was uncommon.

KEYWORDS

Graves' Disease, Ophthalmopathy

Corresponding Author:
Dr. Shaji Ankan,
Department of Ophthalmology,
Government Medical College,
Konni, Kerala, India.
E-mail: shaji.ankan@gmail.com

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BACKGROUND

Thyroid-associated orbitopathy or Graves' ophthalmopathy, is part of an autoimmune process which can affect the orbital and periorbital tissue, the thyroid gland and the pretibial skin or digits. Thyroid eye disease is a relatively rare condition, with an incidence of 2.9 to 16.0 cases per 100 000 population per year. Approximately 50 % of patients with Graves' disease develop clinically apparent thyroid eye disease.[1] The disease is more common in females. The higher preponderance in females relates to the higher incidence of hyperthyroidism in females. However, for severe thyroid eye disease, the ratio of females to males reverses to approximately 1:4[2] most patients are aged 30-50 years, with severe cases appearing to be more frequent in those older than 50 years.[3]

It may cause severe damage to vision and orbital architecture. It is the most frequent cause of unilateral or bilateral proptosis in adults. Sight-threatening complications include optic neuropathy and exposure keratopathy. The presentation of Graves' ophthalmopathy varies among different ethnic groups. Upper lid retraction and soft tissue involvement are reported as the commonest manifestations in Caucasians, whereas exophthalmos and lower lid retraction are common in Asians.[4,5]

Aim

The study aims to detect the proportion and common clinical signs of ophthalmopathy in Graves' disease patients in a tertiary care hospital in Kerala.

METHODS

A cross sectional study of 80 patients with GD was carried out in association with thyroid clinic for a period of 1 year from April 2017 to March 2018. Subjects who have a prior diagnosis of GD including those who were on antithyroid drug were included in the study. Patients who are sick due to other systemic diseases like cardiac failure and end stage renal disease were excluded. Age and sex of patients were noted, comorbidities were recorded. A detailed history of symptoms were taken which included spontaneous and gaze evoked pain, defective vision, redness, diplopia, photophobia, puffy lid and headache. The treatment history was also noted. Examination of lid signs like lid retraction, lid lag, oedema and redness of eyelids were noted. Soft tissue involvement such as conjunctival chemosis, swelling of caruncle and protrusion of orbital fat were noted. Corneal involvement of punctate lesions and ulceration were noted. IOP was measured using applanation tonometer. Extraocular movements assessed and pattern of ocular myopathy observed with or without Hess chart if required. The measurement of unilateral and bilateral proptosis was done using Hertel's exophthalmometer. More than 20 mm or a difference between 2 eyes more than 2 mm was considered to have exophthalmos. Visual acuity, colour vision and presence of relative afferent pupillary defect were noted and it was followed by fundus evaluation to look for signs of optic nerve compression. Visual field central 30-2 was done in affected cases with automated perimetry. Clinical activity of Graves' ophthalmopathy is classified as per clinical activity score recommended by European Group on Graves' Orbitopathy. A clinical activity score of 0 - 2 is considered inactive and 3 - 7 active. Severity is classified into mild, moderate-severe and sight-threatening based on the European Group on Graves' Orbitopathy (EUGOGO) classification.

Sample Size

Sample size was calculated based on the formula
$n = (Z2\ 1 - \alpha/2)\ PQ/d2$
Sample size was fixed as 77.
For the present study it is taken as 80.

Ethical Considerations

- Institutional ethical committee clearance will be obtained.
- Informed consent will be obtained from all participants.
- Confidentiality will be ensured and maintained throughout the study.

Data Analysis

- Continuous variables are reported as mean ± standard deviation (SD) or median (inter-quartile range).
- The Student's t test or Mann-Whitney U test will be used for comparison of continuous variables as appropriate.
- The chi-square test will be used to compare categorical variables.
- Statistical analyses will be performed using the SPSS software version

RESULTS

Out of the 80 patients taken, mean age was 48.5. Majority were females (66.3 %) and males were 33.7 %. Majority of patients had bilateral disease with lid signs (lid retraction in 74.2 %, Lid lag in 51.6 %, lagophthalmos in 16.1 %). Exophthalmos was found in 64.5 %. 50 % had moderate to severe soft tissue involvement. 68.6 % showed some amount of extraocular muscle involvement, movements were full in remaining 31.4 %. Corneal involvement was absent in 63.9 %, punctate keratopathy was present in 30 % and 2.8 % had corneal ulcer or sight threatening disease. Optic nerve dysfunction noted in 3.2 % as shown in table 1 and figure 1.

Feature	Percentage of Patients
Lid retraction	74.2 (59)
Exophthalmos	64.5(52)
Soft tissue involvement	58.1(46)
EOM Restriction	58.1(46)
Dry eye	54.8(44)
Lid lag	51.6(42)
Lagophthalmos	16.1(13)
Diplopia	3.2(3)
Optic nerve dysfunction	3.2(3)

Table 1. Clinical Features in Patients with Ophthalmopathy

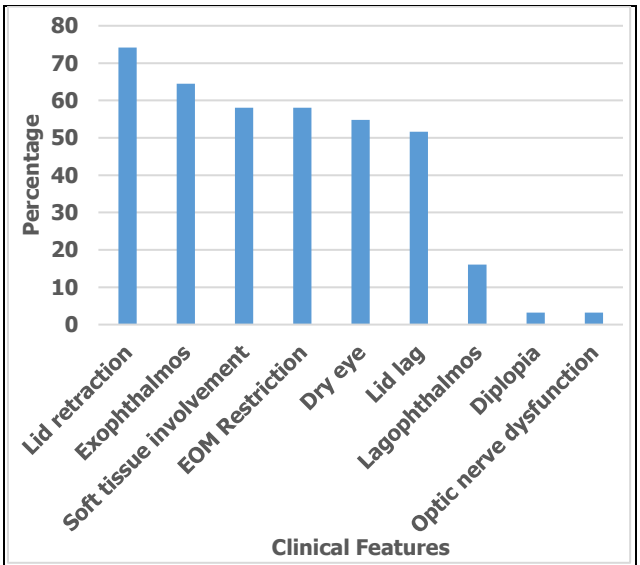

Figure 1. Percentage of Patients with Presence and Absence of Different Clinical Features of Thyroid Ophthalmopathy

	No. of Patients	Percentage
Absent	16	51.6
Punctate erosions	14	45.2
Ulcer	1	3.2

Table 2. Corneal Involvement in Patients with Ophthalmopathy

Sight threatening corneal involvement like ulcer constituted the rarest among clinical features of thyroid ophthalmopathy (3.2 %). Majority had good visual status i.e., 67.5 % had a BCVA > 6 / 12.

Best Corrected Visual Acuity

Best Corrected Visual Acuity (Snellen's Chart)	No. of Patients	Percent	Cumulative Percent
Up to 6/9	54	67.5	67.5
6/12 to 6/60	22	27.5	95.0
less than 6/60	4	5.0	100.0
Total	**80**	**100.0**	

Table 3. Best Corrected Visual Acuity

Smoking showed a significant association with the severity of ophthalmopathy. (p value 0.001) as shown in figure 3 and table 4.

	Total Number of Patients	With Ophthalmopathy	Mild Disease	Moderate to Severe Disease	Sight Threatening Disease	p Value*
Smoker	15	9	2	5	2	0.001
Non- smoker	65	22	17	5	0	

Table 4. Association between Smoking and Severity of Disease

* Chi-square test was used as test of significance

There was a statistically significant association between smoking and severity of disease (p=0.001). There was a significant association between age and activity of disease. (p value 0.021) as shown in table 5

	Clinical Activity	N	Mean	P Value
Age	Active disease	6	59.83	0.021
	inactive disease	25	45.08	

Table 5. Association between Age and Activity of Disease

There was a significant association between age and activity of disease. No association was found between duration of disease with presence or severity of ophthalmopathy. There was no association between co-morbidities with presence or severity of ophthalmopathy. No association was found between hormone status and presence or severity of ophthalmopathy.

No association was found between comorbidities and severity as well as activity of disease. No association was found between smoking and thyroid ophthalmopathy. There was no association of severity as well as activity of disease with TSH value also. 20%patients has active disease (clinical activity score > or = 3).8.3 % has sight threatening disease, 27.7 % has moderate to severe disease and 64 % has mild disease.

DISCUSSION

GD is a complex, multigenic condition. The disease aetiology appears to be a result of many interactions between relatively weak susceptibility genes and environmental factors. Specific genes, such as HLA,[4] CTLA4,[5] TCR beta - chain, and I g heavy chain have been shown to have association with GD, but their relative risk is small. There are a few studies that specifically examined genetic differences between GD patients with GO and GD patients with no apparent eye disease. But these studies did show any confirmed susceptibility loci for GO because these studies confirm that various polymorphisms were seen in GD and they occurred in equal proportion in Graves' patients with and without eye disease.[6] The recent whole genome linkage studies suggested that three interacting loci found on different chromosomes induce genetic susceptibility to GD.[7] These studies concluded that there was no major role for familial factors in the development of severe GO in patients with GD.[8] The investigators in the studies tested four candidate genes, namely HLA, TNF beta, CTLA4, and TSHR, and found that none to be specifically associated with GO. Thus, it was concluded that environmental factors, rather than major genes, are likely to be the primary predisposing factors in the development of GO. Patients with GO are more likely to be women by a 2:1 ratio because women tend to have higher incidence of autoimmunity compared to men. But studies show that men with GD have the same risk of GO development, which is usually of a more severe form but occurs at a more advanced age than in their female counterparts.[9] There are differences in the prevalence of GO in varied ethnic groups with Asians having a lower likelihood of developing the disease than Europeans.[10] The prevalence of smoking among patients with GD is higher than in controls the relative risk of developing GD in relation to smoking is quite small (odds ratio 1.9).[11]

However, the association between smoking and GO has been shown to be much stronger in many studies representing the strongest risk factor known for this

condition. A causal relation between radioiodine treatment and the development of GO is plausible. Autoimmune reactions plays a predominant role in the aetiopathogenesis of GO which occurs in the orbit of GO. In these patients, the immunological process are probably triggered by recognition of the TSH receptor (TSHR) presented to auto reactive T-lymphocytes infiltrating the orbit by antigen-presenting cells, including B lymphocytes and macrophages. TSH receptor is expressed on orbital fibroblasts and adipocytes after their differentiation from pre adipocytes. Other cell surface antigens, i.e. the insulin-like growth factor-1 (IGF-1) receptor (IGF-1R), may also be involved in the initiation or maintenance of orbital autoimmunity. IGF-1R is expressed on orbital fibroblasts, T lymphocytes, B lymphocytes. Interaction of TSHR and IGF-1R are likely required for the development of orbital autoimmunity.[12-14] Histologic studies of Graves' ophthalmopathy have focused on extraocular muscles, owing to their obvious enlargement in patients with the disease.

However, electron microscopy reveals that the extraocular muscle fibers are intact in such patients.[15-18] The extraocular muscles are widely separated by an amorphous accumulation of granular material consisting primarily of collagen fibrils and glycosaminoglycans, among which hyaluronan predominates.[19-21] The polyanionic charge and extremely high osmotic pressure of this matrix substance make it extremely hydrophilic and capable of binding of water many times its weight. Consequently, the muscle bodies become oedematous and may enlarge to many times their normal size. In inactive disease, atrophy and fibrosis of muscle bundles are evident, with extension of fibrous strands into adjacent adipose tissues.[22,23] The same histologic features of thyroid dermopathy are similar to those seen in the orbit, with hyaluronan accumulation in the reticular dermis, although with less abundant lymphocytic infiltration and no evidence of fat expansion.[24] Focal and diffuse mononuclear-cell infiltration occurs within the extraocular and levator muscles, lacrimal glands, and adipose tissues in active Graves' ophthalmopathy. These cells are primarily CD4+ T cells, but there are of CD8+ cells, B cells, plasma cells, and macrophages in minor proportions. In early stages of the disease, type 1 helper T cells predominate and produce the cytokines interleukin-2, interferon γ, and tumour necrosis factor (TNF), indicating ongoing cell-mediated immunity within the orbit. In disease of longer duration, type 2 helper T cells that produce interleukin-4, interleukin-5, and interleukin-10 are dominant and propagate autoantibody production. Macrophages, fibroblasts, and adipocytes produce other inflammatory mediators, including interleukins 1, 6, and 16 and transforming growth factor β (TGFβ) within the orbit.[22]

Recent evidence suggests that orbital fibroblasts are the target cells in Graves'ophthalmopathy.[6] This concept derives from the finding that orbital T cells obtained from patients with Graves' ophthalmopathy proliferate when exposed to autologous orbital fibroblast proteins in vitro. Most orbital disorders are inflammatory, suggesting that orbital fat (12) as well as orbital fibroblasts may be especially prone to inflammatory reactions.[25-27] Although orbital fibroblasts produce high levels of the proinflammatory cytokine interleukin-1, their expression of the neutralizing interleukin-1–receptor antagonist is relatively low.[28] Likewise, orbital fibroblasts treated with interferon γ or leukoregulin synthesize high levels of prostaglandin E2, a mediator with important roles in inflammation.

The cell-surface marker Thy-1 (CD90) is overexpressed in orbital tissues in and produces a population of fibroblasts capable of cytokine induced production of prostaglandin E2, interleukin-8, and hyaluronan.[22,28,29]

In our study 80 patients with GD were included over a period of 1 year. Among the 80 patients, 27.5 % belonged to the age group 41 - 50 years, 26.25 % were in the age group 51 - 60 and least number of patients (2.5 %) belonged to 71 - 80 age group. The mean age was 45.31. In our study also, among the 80 cases females formed majority, 53 cases (66.3 %) and males constituted 27 cases (33.8 %). Hypertension was the most common comorbidity noted in 21 patients (26.25 %) whereas diabetes mellitus constituted 18 cases (22.5 %) and bronchial asthma was noted in 7.5 %. Smokers constituted 18.8 % and all of them were males. Among the total population of 80 patients, 70% were having antithyroid medications (56 patients). TSH levels were normal in 75%. (60 patients). In the remaining 4, TSH levels were controlled with thyroidectomy alone.

Majority retained good vision; that is 67.5 % had a best corrected visual acuity better than 6 / 9 in Snellen's visual acuity charts. Only 5 % had a visual acuity less than 6 / 60. Among the 80 patients with GD, ophthalmopathy was present in 31 patients (38.8 %). In a study conducted by Hiromatsu Y et al in Japan Graves' ophthalmopathy was clinically relevant in 25 – 50 % of patients with Graves' disease.[30] In another report by Lim SL et al, the prevalence was 40 % among Indians residing in Malaysia and 34.7 % altogether.[31]

However, only 10 Indian subjects were included in this study. Whereas in a study conducted by SVB Reddy et al in north India in 235 consecutive adult patients with GD, prevalence of Graves' ophthalmopathy was 28 % which is slightly lower than that of ours.[32] Among these 31 patients with ophthalmopathy, maximum number of patients fell in the middle age group i.e., 41 to 50 and 51 - 60 years which is agreeing with study by Putta Manohar. S et al.[33] Mean age was 47.93 in our study. Our study has a total of 53 females and 27 males. Among them, 18 females and 13 males had Graves' ophthalmopathy. So the prevalence of ophthalmopathy was slightly higher among males, 48.1 % in males and 33.9 % in females. Higher prevalence in males may be because of the higher rate of smoking among males in our population. We haven't got a statistically significant association between age (p value 0.655) or gender (p value 0.144) and severity of ophthalmopathy. But we got an association between age of patients and clinical activity of the disease. (p value 0.014).

According to the study of Perros P et al, there was a positive relationship between age and ophthalmopathy index ($P < 0.001$); after correcting for age, males had an average ophthalmopathy index 41 % greater than that of females.[34,35] Only a few patients (< 2 %)suffered from moderate and severe Graves' ophthalmopathy below the age of 40 years whereas Graves' ophthalmopathy was relatively

common in age groups 40 to 60 year(~8 %) according to a report by Peter Laurberg et al. Among the 31 Graves' ophthalmopathy patients, hypertension and bronchial asthma prevailed (16.1 %) among the comorbidities. No association was found between severity of the disease and comorbidities also (hypertension p = 0.606, bronchial asthma p = 0.395, diabetes p = 0.606). 9 out of 31 patients were smokers. A significant association was obtained between the severity of disease and smoking. (p value 0.001) which is agreeing with previous studies.[11] Among patients with thyroid ophthalmopathy, 74.2 % were taking antithyroid medications. All of them were on carbimazole. But TSH levels were well controlled in 71 % only. No association was found between TSH levels and activity (p value 0.642) or severity (p value 0.643) of disease.

The occurrence of GO in hyperthyroid as well as euthyroid states is well documented in the literature. Major proportion of patients had good visual acuity 6 / 9 or better (64.5 %) only 2 patients had poor visual acuity of less than 6 / 60. (6.5 %) among the 31 patients. In the study by Bartley et al, The most common clinical sign is eyelid retraction (occurs in 90 % of patients with TED, followed by exophthalmos (60 %) and eye movement restrictions (40 %). In the report of SVB Reddy et al, upper eyelid retraction was the most common manifestation 54 (83 %), followed by exophthalmos 49 (75 %) and soft tissue involvement 26 (40 %). In the present study also, lid retraction was the most common manifestation that is 74.2 % followed by exophthalmos (64.5 %) and eye movement restriction and soft tissue involvement 58.1 %), which was consistent with a prior studies in Indians. Soft tissue inflammatory signs were observed with greatest frequency (75 %) in the EUGOGO study.[30]

Diplopia, optic nerve dysfunction and sight threatening corneal involvement like ulcer constituted the rarest among clinical features of thyroid ophthalmopathy (3.2 %) in our study. Only 19.3 % patients had clinically active disease in the current study. Genetic susceptibility is also likely to play a role in the activity and severity of the disease. The severity of Graves' ophthalmopathy and clinical activity is also known to vary with the duration of the disease.[34-37]

CONCLUSIONS

To conclude, our results indicated that the prevalence of ophthalmopathy in our population with GD evaluated at our tertiary care centre was similar to that reported in the Caucasians of European origin. Clinically active and sight threatening ophthalmopathy was uncommon. Majority of patients in our population has mild disease with predominant lid signs. Smoking has a strong association with severity of the disease. Clinically active disease has a significant association with age.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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