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Research Article

Prevalance and Severity of Ophthalmic Manifestations of Graves' disease in tertiary clinic of north India.

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ABSTRACT:

TOPIC: Clinical study of thyroid associated orbitopathy in patients with Graves' disease. INTRODUCTION: Thyroid Associated Orbitopathy (TAO), also known as Thyroid Eye Disease (TED) is most commonly a manifestation of the systemic autoimmune process known as Graves' disease (GD).
AIM: To evaluate the ocular manifestations in patients with Graves' disease. MATERIALS AND METHODS: All patients of Thyroid associated ophthalmopathy seen in our institute were subjected to a complete clinical work up, computed tomography, thyroid 99mTechnetium-pertechnetate scan, triiodothronine, thyroxine, thyroid stimulating hormone and anti thyroid peroxidase antibody assays.
RESULTS: Age of patients ranged from 15-68 years. The male: female ratio was 0.62 :1. Distribution of thyroid dysfunction was hyperthyroidism (73.07%), hypothyroidism(7.69%) and euthyroid(19.23%). Majority of patients had mild (65.4%) moderate to severe in (34.6%) and none of the patients showed any signs of a sight threatening disease. Eyelid retraction was the most common presentation (78%). Other manifestations were proptosis (48.1%), soft tissue inflammation (44%) and elevation defect (5.8%).None of the patients had any evidence of dysthyroid optic neuropathy.The association of smoking with greater severity of thyroid associated orbitopathy was not apparent.
Key Words: Thyroid associated ophthalmopathy, Clinical presentation.

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INTRODUCTION

Thyroid Associated Orbitopathy (TAO), also known as Thyroid Eye Disease (TED) is most commonly a manifestation of the systemic autoimmune process known as Graves' disease (GD). This process affects the thyroid gland, pretibial skin and orbit[1]. TAO is a common orbital disease and is described as a chronic inflammation of orbital and periorbital tissue of most likely an autoimmune origin[2]. TAO is most commonly associated with hyperthyroidism (77%), however patients may be hypothyroid (3%) or euthyroid (20%)[6]. Ophthalmic manifestations are present in up to 50 percent of patients with GD, and patients most commonly present in the 3rd to 5th decade of life with women more commonly affected with A female to male ratio of 5:1 [2]. TAO may precede or follow endocrinologic manifestations, however they typically present within 18 months of each other[1]. TAO occurred before the Graves' disease in 23% concurrent with GD in 39% and after GD in 37%[3]. We designed a study to document the clinical presentation of 52 cases of thyroid associated ophthalmopathy seen in the out-patient department of our department of ophthalmology.

AIM: To evaluate the ocular manifestations in patients with Graves' disease.

MATERIALS AND METHODS: All consecutive adult patients with Graves' Disease who were referred from the Endocrinology clinic of Government Medical College, Srinagar, Kashmir over a period of 1.5 years were enrolled. The hospital is a government, tertiary care referral centre in north Indian State of Jammu and Kashmir. A diagnosis of GD was made on the basis of clinical features of thyrotoxicosis, elevated thyroid hormones, suppressed thyrotropin (TSH) and thyroid 99mTechnetium-pertechnetate scan evidence of diffuse homogeneous increased uptake in both lobes of the thyroid. All patients were provided with written informed consent, and institutional ethics committee approval was obtained prior to the start of the study. In each patient, the initial screening for TAO was performed by an endocrinologist. The patient was referred to the Department of Ophthalmology where a detailed clinical examination for determining the clinical activity and severity was done.

The findings were classified as per the European Group on Graves' Orbitopathy (EUGOGO) recommendations - preliminary case record form. The diagnosis of TAO was based on the criteria of Bartley and Gorman. A measurement of ≥20 mm using a Hertel'sexophthlamometer was diagnosed as exophthalmos. The above cut-off has been previously validated in healthy north Indian population. Clinical activity of TAO was classified as per clinical activity score (CAS) recommended by EUGOGO. A CAS of 0-2 is considered inactive and 3-7 active TAO. Severity of TAO was classified into mild, moderate-severe and sight n threatening based on the EUGOGO classification. All patients who had clinical evidence of orbitopathy underwent CT scan of orbits. Serum total T3, total T4 and TSH were estimated by chemiluminescence immunoassay. Serum thyroid peroxidase antibodies (TPOAb) was measured using radio-immunoassay. A cut-off value of TPOAb ≥20 IU/ml was considered positive. The analytical sensitivity was 2 IU/ml.

OBSERVATIONS AND RESULTS:

Table 1 & 2 show demographics. Age of the study subjects ranged from 15 to 68 years with a mean age of 42.1±11.49 years. As shown in table 1, majority of the patients were clustered in the age group of 45-59 years (46.2%) followed by 30-44 years (34.6%).

There was a female preponderance among the study subjects with 32 females (61.53%) and males (38.46%).

Table 3,4 and 5 show major clinical manifestations of thyroid ophthalmopathy. Conjunctival redness was the most commonly found soft tissue sign seen in 61.5% patients followed by eyelid erythema (44.2%), eyelid swelling (32.7%), plical swelling (23.1%). Only 5.8% patients had chemosis. Lid retraction was the most common ocular manifestation seen in a total of 78%, out of which 61% had upper lid retraction and 55% had lower lid retraction. Lagophthalmos was present in 19.2% because of proptosis. Almost half of the study group (51.9%) had proptosis of >20mm.

Table 6 & 7 show distribution as per severity and activity respectively. Disease was of mild severity in maximum number (65.4%) patients, moderate to severe in 34.6%. None of the patients had any evidence of sight threatening disease. CAS was inactive in 55.8% of the study group and active in 44.2%.

Table 8 depicts the thyroid status of the patients. Majority of the patients were clustered in the hyperthyroid group (73.07%), followed by euthyroid (19.23%) and hypothyroid (7.69%).

Table 1: Age distribution of study patients

Age (years)	**Frequency**	**Percentage**
15-29	8	15.4
30-44	18	34.6
45-59	24	46.2
≥ 60	2	3.8
Total	52	100
Mean±SD=42.1±11.49		

Table 2: Gender distribution of study patients

Gender	**Frequency**	**Percentage**
Male	20	38.46
Female	32	61.53
Total	52	100

Table 3: Soft tissue signs of eyes in the study population

Soft Tissue Signs	No. of eyes	Percentage
Eyelid swelling	34	32.7
Eyelid Erythema	46	44.2
Conjunctival redness	64	61.5
Chemosis	6	5.8
Plical swelling	24	23.1

Table 4: Lid signs of eyes in the study population

Lid Signs		No. of eyes	Percentage
Upper Lid Retraction	0 mm	49	47.1
	1 mm	24	23.1
	2 mm	23	22.1
	3 mm	5	4.8
	4 mm	3	2.9
Lower Lid Retraction	0 mm	46	44.2
	1 mm	20	19.2
	2 mm	16	15.4
	3 mm	7	6.7
	4 mm	7	6.7
Lagophthalmos	Present	20	19.2
	Absent	84	80.8

Table 5: Proptosis of eyes in the study population

Proptosis	No. of eyes	Percentage
< 20	54	51.9
≥ 20	50	48.1
Total	**104**	**100**

Table 6: Severity of disease in study patients as per EUGOGO criteria

Severity of Disease	Frequency	Percentage
Mild	34	65.4
Moderate to severe	18	34.6
Sight Threatening	0	0.0
Total	**52**	**100**

Table 7: Clinical activity score of eyes in study patients

Clinical Activity Score		No. of eyes	Percentage
Inactive	0/7	10	9.6
	1/7	24	23.1
	2/7	24	23.1
Active	3/7	16	15.4
	4/7	10	9.6
	5/7	18	17.3
	6/7	2	1.9
Total		**104**	**100**

Table 8: Thyroid status of study patients

Thyroid Status	No.	%age
Hyperthyroid	38	73.07
Euthyroid	10	19.23
Hypothyroid	4	7.69
Total	**52**	**100**

DISCUSSION:

This study was conducted on patients diagnosed with Graves' Disease, attending our tertiary care centre. We included 52 Patients, age range of 15-68 years with mean age of 42.1+11.49 years. Majority of patients (46.2%) were clustered between 45-59 years of

age. In the study by Marcocci C et al[4] age distribution revealed a peak prevelance in the 5th decade of life, which was comparable to our study. Again in a clinical research of Graves' Ophthalmopathy by Wiersinga W M et al[2] the findings revealed that the mean age of patients was 44.5 years, which was again comparable to our study in which the mean age was 42.1+11.49 years. He JF et al[5] in his study on 339 Chinese patients found out that TAO occurred mostly in individuals over 40 years with no gender preference.

Among the study population with thyroid associated orbitopathy out of total of 52 patients 20 were males that is 38.46% and 32 were females that is 61.53% thus giving a male female ratio of 0.62 :1 . According to western study conducted by Kendler DL et al[6] the male-female ratio was 0.29 in all age groups. Again in the study by Marcocci C et al[4] it was seen that out of 202 patients 67% that is 136 patients were females and 33% that is 66 patients were males with a male female ratio of 0.48:1. The higher preponderance in females relates to higher incidence of hyperthyroidism in females.

In the study group of 52 patients, 38 were found to be of hyperthyroid state (73.07%), 10 euthyroid state (19.23%) and 4 hypothyroid state (7.69%). The mean T3, T4 and TSH levels of the hyperthyroid group was 45.10ng/mL, 18.75ug/dL and 0.065uIU/mL respectively. Again the mean T3, T4 and TSH levels of the hypothyroid group was 5.56ng/mL, 4.63ug/dL and 40.56uIU/mL respectively. Whereas the mean T3, T4 and TSH levels of the euthyroid group was 1.4ng/mL, 6.2 ug/dL and 4 uIU/mL respectively. The mean anti TPO level was 30.1 IU/ml + SD 4.34. The thyroid scan showed a mean Tc99m uptake of 45%. There was increased tracer uptake showing hyperfunctioning thyroid gland which again was suggestive of Graves' disease.In an Indian study by Khurana AK et al[7] the thyroid status of 63.3% of patients was hyperthyroid and 36.7% was euthyroid. Reddy SV et al[8] in their study found out that at the time of enrolment 76% patients were hyperthyroid and 20% euthyroid and 10% hypothyroid. However in a study conducted in Minnesota by Bartley GB et al[1] 90% of the patients had Graves' hyperthyroidism, 1% hypothyroid, 3% thyroiditis and 5% euthyroid.

The EUGOGO established in 1999 developed an assessment protocol for the evaluation of patients with TAO based upon activity and severity parameters. The disease activity is evaluated based on the modified Clinical Activity Score (CAS)[9]. The clinical activity score is based on 7 points on the initial examination and 3 more on follow up. The clinical activity score of our study group was 0/7 – 2/7 in about 58 eyes (55%) i.e. the clinically inactive group and 3/7-7/7 in about 46 eyes (44%) i.e. the clinically active group. Among the soft tissue signs conjunctival redness (61.5%) and eyelid erythema (44.2%) were most commonly seen followed by eyelid swelling (32.7%), plical swelling (23.1%) and chemosis in only (5.8%) of the patients. In a Chinese study by Wang WJ et al[10] which was conducted in 403 TAO cases (676 eyes) TAO with over grade 2 severity was seen in 457 eyes i.e. 67.66% and over grade 4 in 272 eyes i.e. 40.29%. Savko E et al[11], in a study on 306 eyes of 168patients found out that TAO disease was in active phase in 100 eyes (32.6%) and inactive phase in 206 eyes (67.4 %). Mean CAS was 2.21+1.36. However in an Indian study by Reddy SV et al[8]ophthalmopathy was clinically active in only 3% cases.

In a total of 104 eyes upper lid retraction was noted in 52.9% out of which 45% showed a retraction of 1-2 mm and 7.7% had a retraction of 3-4 mm. Lower lid retraction was noted in 48% of eyes, of which 34.6% had a retraction of 1-2 mm and 13.4% had a retraction of 3-4 mm and thus a total of 41 patients out of 52 had lid retraction (78%), out of which

61% had upper lid retraction and 55% had lower lid retraction. Proptosis of greater than or equal to 20mm was seen in 48.1% i.e. 50 out of 104 eyes. Lagophthalmos was present in 20 eyes i.e. 19.2%. The bell's phenomenon was however present and so none of the patients had any signs of keratopathy. According to clinical characteristics of moderate to severe TAO in 354 Chinese cases published in 2017 by Li Q et al[12], it was found that proptosis was seen in 91.24%, eyelid retraction 83.33% out of which 19.77 also manifested lower lid retraction. Because this study included moderate to severe TAO a high percentage of proptosis was seen.

As was seen by Sun H et al[13] upper eye lid retraction was the commonest sign of the lids. Mean extent of proptosis was 17.9 mm. Again He JF et al[5] in their study noted that retraction of eye lids was present in over 70% of cases. Also in a study by Wang YJ et al[10] it was seen that eye lid retraction and lagging eyelids were present in 75.93 and 83.37% cases respectively. Lagophthalmos appeared in 10.42 of the study group. In the study Savko E et al[11] stated that eye lid retraction was seen in 68% of eyes, lagophthalmos in 6.9% and mean hertel'sexophthalmometry value was 20.3+3.2 and proptosis was determined in 47% of the eyes.

In the Indian study by Reddy SV et al[8] upper lid retraction was the most common manifestation (83%) followed by exophthalmos. A plethora of thyroid eye signs have been identified since the original description of the disease. A few eponymic signs, such as von Graefe's (upper lid lag on down gaze) and Dalrymple's sign (lid retraction and scleral show) together with bilateral exophthalmos and enlarged thyroid are virtually pathognomic for endocrine exophthalmos.

Elevation defect was seen in 6 eyes i.e. 5.8% of the study population. No other extra occular muscle abnormality was seen in the subject. It was stated by Wang YJ et al[10] that the CT examination showed that the most common extra ocular muscle involvement was that of inferior rectus; medial rectus and superior rectus was the second and third involved muscles respectively. Lateral rectus was seldom involved. According to Sun H[13] inferior rectus was the most frequently involved with enlargement. In Kendler DH et al[6] study on 557 patients it was found that men had more limited upward duction than women. In 1995 Villadolid MC et al[14] stated that 12 of 17 (71%) of untreated Graves' disease patients with no clinical ophthalmopathy showed extra ocular muscle enlargement on MRI. Apparent enlargement of extra ocular muscle were also detected by MRI in all 11 of Graves' disease patients with clinical ophthalmopathy. Both groups showed the IR muscle as the most frequently involved (56%) and (77%) respectively. In our study group disease was mild in 34 patients i.e. 65.4% moderate to severe in 18 patients i.e. 34.6%, however none of the patients showed any signs of sight threatening disease.

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