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Original Article

Clinical Association of Thyroid Eye Disease with Disease Severity and Thyroid Functional Status-an Experience of a Tertiary Care Hospital, Karachi

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ABSTRACT

Objectives: To determine the occurrence and severity of thyroid eye disease regarding thyroid function in patients with autoimmune thyroid disease (AITD).

Study Design: Cross-sectional study.

Place and Duration of Study: Endocrinology Clinics, Jinnah Postgraduate Medical Centre (JPMC) and Medicell Institute of Diabetes Endocrinology & Metabolism (MIDEM) Karachi Pakistan, from Jan to Dec 2020.

Methodology: Patients with AITD or the presence of eye disease were included in the study. Socio-demographic, clinical and laboratory parameters, including thyroid function tests (TFTs), thyroid autoantibodies (TRAb, Anti-TPO, Anti-Tg), presence or absence of eye disease and its severity according to NOSPECS, were documented on a predefined proforma.

Results: A total of 220 patients with a mean age of 35.58±13.52 years and female predominance were included. Hyperthyroid, Hypothyroid and Euthyroid states were found in 125(56.82%), 43(19.5%) and 6(2.7%) of patients, respectively. Eye disease was found in 59(26.81%) patients. The mean NOSPECS score for patients with Grave's Orbitopathy (GO) for males was 2.56±1.08, and for females, 2.59±1.01. Females had a greater number of TED-related signs and symptoms as compared to men (p=0.01). NOSPECS severity score of TED significantly correlated with fluctuating TFTs and overactive thyroid state (p<0.0001).

Conclusion: Patients with TED commonly presented with proptosis, lid retraction, and restricted movements. The severity of GO was significantly related to older age, female gender, smoking, fluctuating TFTs and hyperthyroidism. Endocrinologists and Ophthalmologists should both work in collaboration for appropriate management.

Keywords: Thyroid eye disease, Grave's ophthalmopathy, Proptosis, Hyperthyroidism, Hypothyroidism, Euthyroidism.

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INTRODUCTION

Thyroid Eye Disease (TED), sometimes more commonly called Grave's Ophthalmopathy (GO), is an inflammatory disfiguring condition of the eyes that can be sight-threatening and debilitating psychosocially.[1] It is the most common extrathyroidal manifestation of autoimmune thyroid diseases (AITD) because of immunoreactivity against thyroid stimulating hormone receptor (TSHR) in both the thyroid and orbit.[2,3] GO occurs in around 40% of individuals with Grave's Disease (GD) and is seen as the common cause of orbital disease in adults with a devastating impact on daily life.[4] Amongst patients with TED, hyperthyroidism is seen in 85% of patients, hypothyroidism in 10% and euthyroidism in 5%.[5] TED commonly affects middle-aged and young females and usually appears within a year of the diagnosis of hyperthyroidism.[6] Risk factors for the patients presenting with TED have been categorized into modifiable and non-modifiable.[7]

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Most patients presenting with GO are treated through medicines, including steroids, azathioprine, or rituximab. However, surgical techniques have been proven more efficient in rehabilitation, especially when vision loss is threatened, and a high inflammatory phase is involved.[8] In the early stages of the disease, patients present with swelling of eyelids, puffiness, dryness of eyes and retraction of upper or lower eyelids, with the progression of the disease manifesting as double vision, excessive proptosis, squinting of eyes and restriction of eye movements.[9,10]

TED is a significant cause of morbidity in patients with Graves' disease. This study aimed to determine the occurrence and severity of TED and its association with thyroid functional status in patients in Karachi, a population with diverse ethnicity from all over Pakistan.

METHODOLOGY

The cross-sectional study was conducted at the Endocrinology Department, Medical Institute of Diabetes Endocrinology & Metabolism (MIDEM) and Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan, from January to December 2020. The sample

size was calculated using the select statistics sample size calculator. Ethical approval was obtained from the Institutional Review Board of MIDEM and JPMC before the study (IRB-002/MHS/19 and NO.F.2-81/ 2019-GENl/3419/JPMC), and informed consent was taken from all patients. By keeping the incidence of hyperthyroidism at 85% in patients with thyroid eye disease,[5] a margin of error of 5%, and a confidence level of 95%, a sample size of 217 was obtained.

Inclusion Criteria: Patients with Grave's Disease (GD) or a positive result for one of the three antibodies (TRAb, Anti-TPO and Anti-Tg) were included in the study.

Exclusion Criteria: Patients with primary thyroid dysfunction whose antibodies were negative were excluded from the study.

Patients were classified into the following groups, i) Euthyroidism, ii) Hyperthyroidism, iii) Hypothyroidism, iv) Subclinical Hyperthyroidism, v) Subclinical Hypothyroidism and vi) Fluctuating TFTs. Socio-demographic, clinical and laboratory parameters, including TFTs (FT3, FT4, TSH), Thyroid Autoantibodies (TRAb, Anti-TPO, Anti-Tg), presence or absence of eye disease and its severity according to NOSPECS,[11] were documented on a predefined proforma. The NOSPECS criteria is an important memory aid for staging the severity of Grave's eye disease. There are a few other classification systems for GO assessment, such as EUGOGO and VISA classification systems.[11] Patients were monitored with TFTs as per ATA guidelines.[12]

Data were analyzed using Statistical Package for the social sciences (SPSS) version 26. The qualitative variables were presented as frequencies and percentages. The quantitative variables like age and eye disease severity were presented by their mean±SD. The comparison of proportions was performed using the chi-square test of proportion. For the comparison of mean values, t-test was used. The *p*-value of ≤ 0.05 was considered significant.

RESULTS

A total of 220 patients with a mean age of 35.58 ± 13.52 years were included. Female patients were predominant in this study. The demographic characteristics are illustrated in Table-I. More than half the patients were hyperthyroid (56.8%) (Figure). In addition, two patients initially presented with gestational thyrotoxicosis and later developed frank hyperthyroidism with positive autoantibodies. Table-II shows the signs and symptoms of patients with thyroid eye disease.

Table-I: Demographics of the Study Participants (n=220)

Characteristics	n(%)
Mean Age (in years) Mean±SD	35.58±13.52
Age Groups	
Less than 30 years	69(31.5%)
30-44 years	95(43.4%)
45 years and older	55(25.1%)
Gender	
Male	38(17.4%)
Female	181(82.6%)
Mean Weight (in kilograms)	62.18±15.67
Mean Height (in centimeters)	157.03±14.3
Mean Body Mass Index (kg/m2)	25.18±5.47
Smoking Status	
Yes	15(6.82%)
No	205(93.18%)
Frequency of Eye Disease	59(26.81%)
Mean Duration of Eye Disease (months) Mean ± SD	28.37±38.434

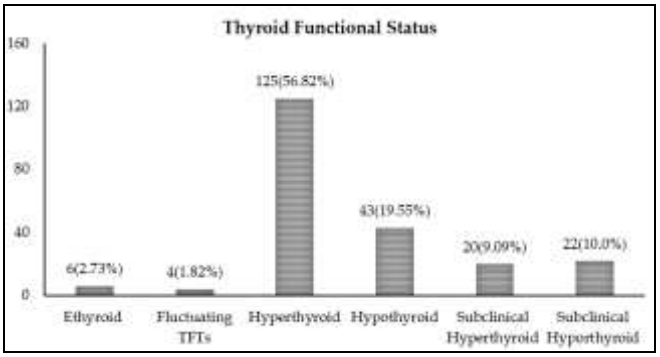

Figure: Thyroid Functional Status of the Study Participants (n=220)

Table-II: Clinical Signs and Symptoms of Patients with Thyroid Eye Disease (n=59)

Characteristics	n(%)
Orbitopathy symptoms	
Bulging/Prominent eyes/Starry Gaze	38(64.4)
Dry eyes (grittiness, irritation)	25(42.3)
Pain in Retrobulbar Region	23(38.9)
Redness and Watery eyes	22(37.2)
Periorbital Swelling	20(33.8)
Diplopia	15(25.4)
Photophobia	12(20.3)
Blurred Vision	8(13.5)
Orbitopathy signs	
Proptosis	42(71.1)
Lid Retraction	38(64.4)
Restricted Gaze	35(59.3)
Lid Lag	33(55.9)
Lid Oedema	20(33.8)
Chemosis	12(20.3)

We reported a mean NOSPECS score for males as 2.56±1.08, and females, it was 2.59±1.01. Furthermore, it was noted that older patients (>45 years) had a greater number of TED-related signs and symptoms per patient as compared to the younger patients (p<0.001). Females had a greater number of TED-related signs and symptoms as compared to men (p=0.01). As indicated by NOSPECS, clinical severity was significantly associated with increasing age (p<0.001). Table-III demonstrates the association between thyroid function status and eye disease severity. It reflects the significant association of severe TED with hyperthyroidism and fluctuating TFTs. Three (75%) of the four cases of fluctuating TFTs had stage 4 TED, while 26 (21.1%) hyperthyroid patients had stage 3 TED. Half the patients in euthyroid patients had no signs and symptoms of TED. (p<0.0001). The study found a significant association between smoking and thyroid eye disease (p<0.001) (Table-IV). Most patients who smoked had severe eye disease (p<0.001).

Table-III: Association of Severity of Eye Disease with Thyroid Functional Status (n=220)

Functional Status	No of cases (n)	Severity of Thyroid Eye Disease						*p*-value
		0	1	2	3	4	5	
Euthyroid	6	3 (50%)	0 (0.00%)	0 (0.00%)	2 (33.3%)	1 (16.7%)	0 (0.00%)	<0.0001
Fluctuating TFTs	4	1 (25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (75%)	0 (0.00%)	
Hyperthyroid	125	76 (60.8%)	10 (8%)	5 (4%)	26 (20.8%)	7 (5.6%)	1 (1.8%)	
Hypothyroid	43	39 (90.7%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7%)	1 (2.3%)	
Subclinical hyperthyroid	20	20 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Subclinical hypothyroid	22	22 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	

Table-IV: Smoking Status and Eye Disease (n=220)

Smoking Status	Eye Disease		*p*-value
	Yes	No	
Positive	15(25.42%)	0(0.00%)	<0.001
Negative	44(74.57%)	161(100.00%)	

DISCUSSION

This study aimed to determine the frequency and severity of TED and its association with thyroid functional status. Thyroid Eye Disease is one of the most common inflammatory diseases of the orbit. 13 Even Though the pathophysiology of the disease is not clear, identification of risk factors and genetic research could play a major part in finding new therapeutic options.

Most of the patients in this study were females (82.6%), with a mean age of 35.58±13.52 years, similar to the previously published demographics of the patients with autoimmune thyroid disease.14 Amongst the patients with thyroid autoimmunity (any of the three antibodies positivity), the majority had a hyperthyroid functional status (67.73%) in this study, possibly because GD has a female preponderance, and TED has a strong correlation with GD.

The prevalence of TED among patients with thyroid dysfunction ranges from 51.7% in the Caucasian population to 34.7% in the Asians. 15 A recent meta-analysis and systematic review of 57 studies, including 26,804 patients, reported an overall prevalence of 40%, whereas an analysis of our region reported a prevalence of 35% in Southeast Asia.[16] An Indian study reported a 28% prevalence of TED with no gender difference, similar to the frequency of GO (26.81%) found in this study. 17 Another study in a multi-ethnic Malaysian population reported a relatively higher prevalence rate of 34.7%.[18] Thus, the overall prevalence of TED, regardless of its severity, can range between 25% and 40% in patients with thyroid autoimmunity.

The frequency of symptoms of eye disease with regards to bulging/prominent eyes and dry eye symptoms, such as grittiness and irritation, is in keeping with what has been reported from India by Murlidhar et al. 15 The severity and prevalence of ocular symptoms and signs in GD published by Gharib et al. reported proptosis as the most common sign in 63.8% of the patients; this was also the case in our study (71.1%).[19]

TED impacts the quality of life about mental health in the form of anxiety, depression, visual disability and cosmetic concerns due to orbit and facial deformities. In a study of patients in the US with mild to severe TED, the quality of life was significantly

affected equally by the moderate and severe symptoms of TED. Early detection and treatment of TED can lead to a better quality of life as well.

This study aids in determining the importance of evaluating every patient with autoimmune thyroid disease for associated eye manifestations and grading its severity so that it can be managed promptly, as the pharmacological options available so far are limited. Furthermore, there is scarce loco-regional data on this significant sight-threatening disease, which also has a detrimental impact on the quality of life.

LIMITATIONS OF THE STUDY

Due to limited resources, doing all three antibodies in each patient was impossible. A long-term follow-up was also not possible.

CONCLUSION

Patients with thyroid eye disease commonly presented with proptosis, lid retraction, and restricted movements. The severity of the disease was directly related to an older age, female gender, smoking and thyroid functional state (hyper-thyroidism and fluctuating TFTs). Therefore, close moni-toring of TED should be done between ophthalmologists and endocrinologists to prevent serious complications and early referral.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

BR: & TA: Supervision, Conception, Study design, analysis and Interperitation of data, Critically reviewed manuscript & approval for the final version to be published.

WA: Critically reviewed, Drafted manuscript & approval for the final version to be published.

PI: & SF: Data colllection, Entry and analysis of data, preparation of rough draft & approval for the final version to be published.

RJ: Data collection and entry & approval for the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investi-gated and resolved.

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