Original Article

Clinical profile of thyroid eye disease and factors predictive of disease severity

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Purpose: To describe the clinical features of thyroid eye disease (TED) in patients presenting at a tertiary eye care centre in North India and to identify factors predictive of severe disease. **Methods:** This observational cross-sectional study involved clinical evaluation of all patients with TED who presented at the oculoplastic clinic based on the ITEDS VISA proforma. Risk factors for the severe disease were assessed using univariate and multivariate logistic regression. **Results:** A total of 106 patients (50 males, 56 females; mean age 41.30 ± 14.76 years) were identified during the study period, 46.23% hyperthyroid, 33.96% hypothyroid and 19.81% euthyroid. The proportion of the patients with hypothyroid was higher as compared with prior studies and most patients with hypothyroid had the mild disease (63.89%). Orbitopathy symptoms were the presenting feature leading to the diagnosis of systemic thyroid abnormality in 25% of the patients with hypothyroid and 59.18% of the patients with hyperthyroid, respectively ($P < 0.05$). Eyelid and orbitopathy signs were more common in the patients with hyperthyroid (51.2% and 87.7%) as compared with hypothyroid where the commonest presenting symptoms were related to dry eye (50.1%). Active disease was seen in 22.6% of the patients. Mild, moderate to severe and sight-threatening disease was seen in 54.7%, 37.7% and 7.5%, respectively. On multivariate analyses, hyperthyroid status and activity was associated with severe disease. Smoking was not associated with activity or severity. **Conclusion:** There is no significant difference in the gender profile of the patients with TED in this cohort. The patients with hypothyroid have a milder disease compared to the patients with hyperthyroid, and dry eye symptoms are the commonest presenting symptoms in hypothyroid subjects. Hyperthyroidism and activity were associated with severe and sight-threatening disease.

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Thyroid eye disease (TED) is a potentially sight-threatening ocular disease mostly occurring in the patients with hyperthyroidism or a history of hyperthyroidism due to Graves' disease (GD). The prevalence of TED among the patients with thyroid dysfunction ranges from 51.7% in the Caucasian population to 34.7% in the Asian population.[1,2] There are known to be ethnic differences in both the clinical presentation and severity of disease with lower eyelid retraction, dry eye and a milder disease course reported frequently in Asians.[3-6] These differences warrant the need for studies that provide data on clinical presentation in different geographical regions. Additionally, to the best of our knowledge, in the geographic region of North India, there are only two studies on clinical profile of TED and both were conducted on a small group of patients.[3,7] This study aims to analyze the demographic profile and clinical manifestations of TED in patients presenting to a tertiary eye care center in North India over 18 months. Additionally, it aims to identify the risk factors that predict disease severity in the patients with TED.

Methods

This was an observational, cross-sectional study conducted at a tertiary eye care hospital in North India. Patients diagnosed with TED as per the Bartley and Gorman criteria amongst those who presented to the out-patient department from August 2017 to January 2019 were included in the study.[8] If lid retraction was seen, the presence of laboratory evidence of thyroid dysfunction, exophthalmos, optic nerve dysfunction or extra ocular muscle involvement was considered as TED. In case of no lid retraction in a patient with laboratory evidence of thyroid dysfunction, the presence of exophthalmos, optic nerve involvement or restrictive myopathy was considered as TED. Patients in whom diagnosis was uncertain or who refused complete ocular examination were excluded from the study. The guidelines of the Declaration of Helsinki were complied with and the Institutional Ethics Committee clearance was obtained. Written informed consent was obtained from all participants.

Data were collected using a self-administered questionnaire and complete ocular examination was recorded as per the ITEDS case proforma.[9] This included demographic data and a history of smoking and comorbidities with an emphasis on autoimmune diseases, systemic thyroid status, orbitopathy status with regards to onset, duration and laterality of symptoms. Objective clinical assessment was done using the VISA (vision, inflammation,

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strabismus and appearance) score assessment. Vision (aided/unaided) was recorded using the Snellen chart; color vision using the Ishihara plates (15 of 38 plates). The afferent pupillary defect was assessed by swinging flashlight test. Optic disc was assessed by slit-lamp biomicroscopy for the presence of edema and/or pallor. Slit-lamp examination was done to look for signs of inflammation namely caruncular oedema, chemosis, conjunctival redness, lid redness and lid edema.

Ocular ductions were graded using the Hirschberg reflex. Various measurements such as margin reflex distance1 (MRD1), palpebral fissure height (PFH), scleral show, levator function and lagophthalmos were recorded in millimeters. Proptosis was measured using Hertel's exophthalmometer. The eyeball was said to be proptosed if Hertel's reading was over 20 mm or there was a greater than 2 mm difference in degree of proptosis. Schirmer's test without topical anaesthesia (for 5 minutes) was done to detect dry eyes.

Based on the VISA score calculated, a score over >4/10 was classified as clinically significant active disease, while a VISA score of ≤4/10 was defined as clinically insignificant quiescent disease. Grading of severity was done by EUGOGO classification for severity and patients were classified to have mild, moderate to severe and sight-threatening disease. Various clinical presentations of TED are depicted in Fig. 1.

Statistical analyses were performed using Microsoft excel office version 2016 and SPSS trial version 23.0 (SPSS Inc., Chicago, IL, USA) software. Quantitative data were expressed as mean ± SD, whereas qualitative data were expressed as percentage and proportions. A significance of difference in means was inferred by student's *t*-test and paired-T test, whereas a significance of difference in proportions was inferred by Chi-square test. Risk factors for severe disease were assessed using univariate and multivariate logistic regression. For significance, $P \leq 0.05$ was considered and all *P* values were two sided.

Results

From August 2017 to January 2019, a total of 106 patients were diagnosed with TED. The baseline characteristics are enlisted in Table 1. The female to male ratio in our study was 1.12:1. The majority of patients belonged to the age group of 41-60 years. Smokers constituted 25.5% of our study population.

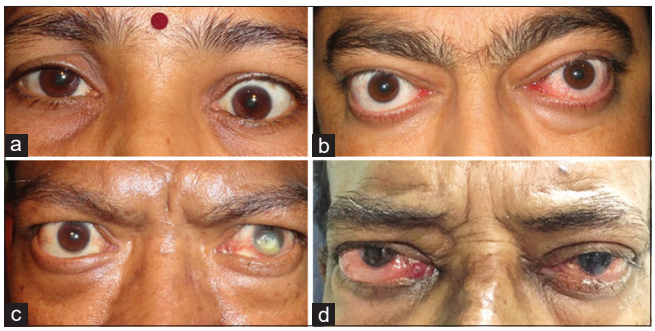

Figure 1: Clinical presentation of thyroid eye disease. Mild inactive thyroid eye disease with left upper eyelid retraction (a). Moderate to severe active disease with left eye conjunctival congestion, chemosis, caruncular edema, eyelid oedema and erythema (b). Sight-threatening eye disease causing corneal exposure keratopathy and infiltration due to severe lagophthalmos (c) and right eye compressive optic neuropathy in a bilateral active thyroid eye disease patient (d)

The most common comorbidity found was hypertension (19.8%) followed by diabetes mellitus (15.1%). Autoimmune disorders which included myasthenia gravis, vitiligo, rheumatoid arthritis, alopecia and psoriasis were seen in seven patients (6.6%).

Among those who were diagnosed with systemic thyroid disease, that is, 46 patients (54.8%) were diagnosed before the onset of eye complaints. Hyperthyroid, hypothyroid and euthyroid status were found in 46.23%, 33.96% and 19.81% of patients, respectively. There was a significantly larger number of patients with hypothyroid diagnosed with systemic thyroid disease before orbitopathy symptoms ($P = 0.001$). In contrast, most hyperthyroid patients were diagnosed with systemic hyperthyroidism after the onset of eye symptoms ($P = 0.002$).

The most common presenting complaint was prominent eyes (65.1% patients). Dry eye symptoms such as epiphora and grittiness with burning sensation were seen in 50.9% and 43.4% of patients, respectively. [Table 2]. Diplopia was observed in 23.6% of our patients. Disabling diplopia in the primary gaze was seen in only five patients (4.7%). The commonest presenting sign was proptosis (64.1%) followed by upper lid retraction (63.2%). Sight-threatening complications such as optic neuropathy, exposure keratopathy and spontaneous globe luxation were seen in 3.7%, 0.9% and 1.9%, respectively.

Table 1: Baseline characteristics and demographic data of the patients with thyroid eye disease

Parameters	Value
Number of patients	106
Age in years (mean±SD)	41.30±14.76
Gender	
No. of males	50 (47.2%)
No. of females	56 (52.8%)
Smoking status	
No. of smokers	27 (25.5%)
Active	20 (74.1%)
Passive	7 (25.9%)
Comorbidities	
HTN	21 (19.8%)
DM	16 (15.1%)
Autoimmune Disease	7 (6.6%)
Family history	
Family history of autoimmune disease	14 (13.2%)
Family history of thyroid disease	24 (22.6%)
Timing of diagnosis	
No. of patients diagnosed with systemic thyroid disease before orbitopathy symptoms	46 (54.8%)
No. of patients diagnosed with systemic thyroid disease after orbitopathy symptoms	38 (45.2%)
Systemic thyroid status	
Hypothyroid	36 (33.96%)
Hyperthyroid	49 (46.23%)
Euthyroid	21 (19.81%)
Laterality	
Unilateral disease	19 (17.9%)
Bilateral disease	87 (81.1%)

In patients with lid retraction, only upper lid retraction was seen in 31 patients (29.2%), only lower lid retraction in 30 patients (28.3%), whereas both upper and lower lid retraction were seen in 36 patients (34%).

The mean VISA inflammatory index of our cohort was 2.15 ± 2.35 (range: 0-7). Clinically significant active disease was seen in 24 patients (22.6%) whereas inactive disease was seen in 82 patients (77.4%). Mild disease was seen in 58 patients (54.7%), moderate to severe disease in 40 patients (37.7%) and sight-threatening disease was seen in eight patients (7.5%).

The independent variables for variate analyses are enlisted in Table 3. The dependent variables analysed included severity of disease. Hyperthyroid status (*OR*: 4.606, *CI*: 1.576-13.458) and activity (*OR*: 7.980, *CI*: 1.920-33.161) were found to be significantly associated with severe disease on both univariate and multivariate analyses [Tables 3 and 4].

Discussion

This observational cross-sectional study describes the clinical characteristics of 106 cases of TED that presented to a tertiary eye care centre in North India over 1.5 years. The female to male ratio in our cohort was 1.12:1 with a mean age of 41.30 ± 14.76 years. The percentage of smokers in our population was 25.5% of which majority (74.1%) were active smokers and the rest were passive smokers. Most were hyperthyroid (46.23%) but a large proportion was hypothyroid (33.96%) and euthyroid (19.81%) as well. Prominent eye (65.1%) and difference in eye size (59.4%) were the commonest complaints. Dry eye symptoms such as epiphora and grittiness with burning sensation were seen in 50.9% and 43.4%, respectively. Bilateral disease was seen in 81.1% and the commonest presenting sign was proptosis (64.2%). Active disease was seen in 22.6% of the patients. With regards to severity, mild, moderate to severe and sight-threatening disease was seen in 54.7%, 37.7% and 7.5% of the patients, respectively. On multivariate analysis, disease activity and hyperthyroid status were found to be significantly associated with severe disease.

Similar to other studies, the majority of patients in our study were female (52.8%) but the female to male ratio was calculated as 1.12:1 that was much lesser than that reported in major Caucasian studies by the EUGOGO who found them to range from 3.34:1 in their first multicentric study to 3.41:1 in the subsequent study.[10,11] On the other hand, ratios cited in Asian studies were similar to our cohort. The study by Lim S.L *et al.* in a multi-ethnic Malaysian population found the female to male ratio as 1.5.[2] A similar value of 1.76 was reported by Lim C.S. *et al.* in a Southeast Asian population in their study.[4] This ethnic difference in female to male ratios was highlighted by Khurana *et al.*in 1992 who found it as 1.5:1.[7] Although there was a slight female preponderance in our study population, the difference was not as stark as that in the Caucasian population. The lower health seeking behaviour of females in our country due to various sociocultural norms could be a contributing cause.[12]

The mean age of our cohort was 41.30 ± 14.76 years. This was less than that reported in the EUGOGO studies (48 ± 14 and 49 ± 13 years) but very similar to that reported in a Southeast Asian population (40.2 ± 15.5 years).[4,10,11] The majority of patients fell in the age group of 41-60 years, which was in keeping with that seen in the Southeast Asian population.[4]

Table 2: Clinical features and the signs and symptoms of eye disease among the study participants

	No. of patients	% distribution
1. Orbitopathy symptoms		
Prominent eyes	69	65.10%
Difference in eye size	63	59.40%
Epiphora	54	50.90%
Lid swelling	52	49.10%
Dry eyes (grittiness, burning)	46	43.40%
Redness	37	34.90%
Diplopia	37	34.90%
Retrobulbar ache	37	34.90%
Diurnal variation	37	34.90%
Lid stare	34	32.10%
Light sensitivity	18	17.00%
Blurring of vision	12	11.30%
Colours appear less bright	2	1.90%
2. Orbitopathy signs		
Proptosis	68	64.15%
Lid retraction (upper lid)	67	63.21%
(a) Upper lid retraction only	31	29.25%
(b) Lower lid retraction only	30	28.30%
(c) Both	36	33.96%
Lid lag	64	60.38%
Restricted movements	50	47.17%
Lagophthalmos	47	44.34%
Lid oedema	44	41.51%
Conjunctival redness	40	37.74%
Punctate epithelial erosions	36	33.96%
Abnormal Schirmers	25	23.58%
Lid redness	22	20.75%
Chemosis	21	19.81%
Caruncular oedema	19	17.92%
Raised IOP in either eye	9	8.49%
Colour vision defects	4	3.77%
Dysthyroid optic neuropathy	4	3.77%
Spontaneous globe luxation	2	1.89%
RAPD	1	0.94%
Optic disc oedema	1	0.94%
Superior limbic keratoconjunctivitis	1	0.94%
Exposure keratopathy	1	0.94%

The percentage of smokers (both active and passive) in our cohort was 25.5% which was much lesser than that reported in Caucasian studies.[10,11] Although smoking is shown to be a strong modifiable risk factor in most studies, it was not found to be associated with the severe disease in our study. This may be attributed to the small sample size of the present study.

Autoimmune disorders have been reported to occur frequently with TED. A large prospective study by Ferrari *et al.* in 2018 found that in patients of Graves' disease with TED, other autoimmune disorders were seen more frequently (18.9%) compared to those without TED (15.6%).[13] The autoimmune disorders seen most commonly in their study

Table 3: Factors predictive of moderate to severe and sight-threatening eye disease (univariate logistics regression analysis)

Factors	Values	ß	Odds ratio	95% C.I. for odds ratio		*P*
				Lower	Upper	
Age	Continuous variable	0.052	1.054	1.022	1.086	0.001
Gender	Female	−0.829	0.437	0.2	0.954	0.038
	Male		1			
Smoker*	Yes	0.759	2.136*	0.878	5.199	0.094*
	No		1			
Hypertensive	Yes	1.371	3.939	1.389	11.172	0.01
	No		1			
Diabetes Mellitus	Yes	1.504	4.5	1.345	15.055	0.015
	No		1			
Autoimmune disease	Yes	0.511	1.667	0.354	7.841	0.518
	No		1			
Family history of auto-immune disease	Yes	0.895	2.446	0.76	7.872	0.134
	No		1			
Family history of thyroid disease	Yes	0.462	1.587	0.636	3.96	0.322
	No		1			
Duration of orbitopathy symptoms	Continuous variable	0	1	0.998	1.001	0.826
Euthyroid	Yes	−0.623	0.537	0.197	1.462	0.223
	No		1			
Systemic thyroid disease diagnosed after TED	Yes	−0.298	0.742	0.313	1.758	0.498
	No		1			
Hyper vs Hypothyroid disease	Hyperthyroid	0.858	2.359	0.974	5.714	0.057
	Hypothyroid		1			
Hyper vs non-hyperthyroid	Hyperthyroid	0.903	2.467	1.125	5.407	0.024
	Non-hyperthyroid		1			
Activity	Active disease	2.657	14.259	3.908	52.031	0.000
	Inactive disease		1			
VISA activity score	Continuous variable	0.682	1.978	1.507	2.597	0.000

Table 4: Factors predictive of moderate to severe and sight-threatening eye disease (multivariate logistics regression analysis)

Factor	Values	ß	Odds ratio	95% CI for odds ratio		*P*
				Lower	Upper	
Age	Continuous variable	0.031	1.031	0.995	1.069	0.089
Gender	Female	-0.496	0.609	0.191	1.937	0.401
	Male		1			
Smoker	Yes	0.302	1.352	0.359	5.095	0.656
	No		1			
Hypertensive	Yes	1.209	3.349	0.779	14.394	0.104
	No		1			
Diabetes Mellitus	Yes	0.678	1.970	0.398	9.753	0.406
	No		1			
Hyper vs non-hyperthyroid	Hyperthyroid	1.527	4.606	1.576	13.458	0.005
	Non-hyperthyroid		1			
Activity	Active disease	2.077	7.980	1.920	33.161	0.004
	Inactive disease		1			

were vitiligo (2.6%), chronic autoimmune gastritis (2.4%), and rheumatoid arthritis (1.9%). Our results are similar to this study. The proportion of patients with other autoimmune disorders in our study was much greater than that reported by Lim CS *et al.*, who found seven patients (0.04%) with autoimmune disorders in their cohort of 174 patients.[4] Our results were comparable to the proportion found in both the major EUGOGO studies, which found it as 5.9% (2012) and 9% (2000).[10,11]

A large proportion of patients in our study were hypothyroid (33.96%) and euthyroid (19.81%). This was much higher than that reported by EUGOGO who had only 3% hypothyroid and 2.9% euthyroid patients.[11] It was also much higher than that reported by studies from Southeast Asia (2.3% hypothyroid, 11.5% euthyroid) and China (4.5% hypothyroid, 11.3% euthyroid).[4,14] In a study from India by Khurana *et al.*, there were 36.67% patients with euthyroid and none had hypothyroidism.[7] Since the most patients could not afford an antibody profile, subclinical disease could have been missed since antibodies can be positive in the presence of normal thyroid status.[15] Also, most hypothyroid patients had a mild disease (63.8%) while most hyperthyroid patients had moderate to severe or sight-threatening disease (56.9%). The classical and easily detectable eyelid and orbitopathy signs were more common in the patients with hyperthyroid (51.2% and 87.7%) compared to hypothyroid where the commonest presenting symptoms were dry eye related (50.1%). Hence, it is possible, milder symptoms like dry eye and mild eyelid retraction can be missed if TED is not suspected in these patients. It can lead to underestimation of the proportion of hypothyroid patients with mild disease especially if the study is retrospective and based in endocrine clinic where clinical suspicion for eye disease might not be high in the absence of the classical signs of proptosis and lid retraction. Ours being a prospective study from a tertiary care oculoplastic clinic with evaluation done by trained oculoplastic surgeon, a higher clinical suspicion and a detailed evaluation for early and milder signs can account for the higher proportion of patients with mild disease in this study. Since mild disease was more common in the patients with hypothyroid, this study consequently has a higher proportion of hypothyroid patients with eye disease as compared with the previous studies. In our study, dry eye symptoms like watering and burning sensation were seen in 50.9% and 43.4% of the patients, respectively. Khurana *et al.* have also reported watering (80%) and gritty sensation (53.3%) as the commonest presenting symptoms among Indian patients with TED.[7] This was greater than that reported in a Southeast Asian population where ocular irritation, epiphora and photophobia were seen in 29.3%, 19.1% and 7.5% of the patients, respectively.[4] Abnormal Schirmer's were also seen in 23.6% of the patients of the cohort. It emphasizes the need for a higher clinical suspicion especially in cases with dry eye symptoms with subtle eyelid signs, which might otherwise get treated as dry eye disease and the diagnosis of TED can be missed.

Upon comparing the other clinical and demographic features of hypo- and hyperthyroid orbitopathy, it was observed that hypothyroid orbitopathy occurred more frequently in females ($P = 0.059$) which was in keeping with previous studies.[16,17]

A majority of hypothyroid patients (75%) presented with systemic hypothyroidism before the onset of orbitopathy symptoms. This was in contrast with the patients with hyperthyroid, most of whom (59.18%) presented with orbitopathy symptoms first. This difference was found to be significant on analysis ($P < 0.05$). In addition, mild disease was seen in a greater proportion (63.89%) of patients with hypothyroid orbitopathy compared to the patients with hyperthyroid orbitopathy ($P = 0.055$). Multivariate analysis for severity showed hyperthyroidism to be significantly associated with severe TED when compared with euthyroid and hypothyroid status. This suggests that hyperthyroid patients present with earlier and more severe orbitopathy features than those with hypothyroid orbitopathy, a finding reported previously by Eckstien *et al.* who found hyperthyroid orbitopathy to have more severe symptoms as well as more active and asymmetrical disease when compared with euthyroid and hypothyroid orbitopathy.[18] These findings emphasizes the need for more closer follow up and frequent ocular evaluation in patients with new onset hyperthyroidism to promptly detect and initiate appropriate treatment for severe and sight-threatening disease. However, Tanda ML *et al.* in their observational study on newly diagnosed patients with Graves' disease have found 74% of patients having no orbitopathy symptoms at presentation and only a minority of them progressing to develop orbitopathy symptoms during follow-up.[19] Similar findings were reported from Danish population in a study by Laurberg P *et al*.[20] Hence, patients with hyperthyroid, who develop moderate to severe orbitopathy symptoms, are likely to develop it at the onset of disease and progression of mild orbitopathy symptoms is minimal.

Most of our patients had bilateral disease at presentation (81.1%). The proportion of bilateral disease was however lesser than that reported in other studies. The most recent study by EUGOGO reported bilateral disease in 87.68% of their patients.[11] Among the Asian studies, Lim CS *et al.* reported bilateral disease in 95.4% of the patients.[4] The pre-existing study by Bhaskar *et al.* found bilateral disease in 97% of the patients with Graves' ophthalmopathy.[3] Since unilateral disease at presentation has been shown to be bilateral on imaging or become bilateral on long term follow up, a prospective long-term study would have been better equipped to comment on this aspect.[21,22]

Upper eyelid retraction was noted in 63.2% and lid lag in 60.4% of our patients. Lower lid retraction was noted in isolation in 28.3% and along with upper eyelid retraction in 34% patients. This was similar to most other Asian studies which found isolated lower lid retraction in 44.3% and both upper and lower lid retractions in 23% of patients.[4] This clinical feature was not reported in the previous Indian studies. In view of the large proportion of patients with isolated lower eyelid retraction, we believe this feature should be considered as a part of the diagnostic criteria for TED.

EUGOGO in its first multicentric study found mild, moderately severe and sight-threatening disease in 40%, 33% and 28% of their patients, respectively.[10] Other studies among the Caucasians population reported the incidence of sight-threatening orbitopathy to range from 0.3% to 12.9%.[19,23] In our study, the mild disease was seen in greater proportion of patients (54.7%) moderate to severe disease was found in 37.7% but patients with sight-threatening disease were significantly lesser (7.5%) than that reported by EUGOGO. Asian studies such as by Lim CS *et al.* found mild, moderate and severe disease to occur in 71.3%, 20.7% and 8.0% of patients belonging to a Southeast Asian population.[4] Although our study had a similar proportion of patients with sight-threatening disease, it had a greater proportion of patients with moderate to severe disease compared to the above study. Studies in the Indian population by Bhaskar *et al.* found majority of the patients to have mild disease (83%) with 15% and 2% patients having moderate to severe and sight-threatening disease, respectively.[3] Our study

found a much larger proportion of moderate to severe and sight-threatening disease compared to this study. This could be explained by the study being conducted at a speciality clinic in a tertiary eye care centre where most patients are referred. As mentioned previously, activity and hyperthyroid status were found to be significantly associated with severe disease emphasizing the need for close follow up and ocular evaluation of all patients with hyperthyroid as well as prompt and appropriate treatment of active disease. It was also observed that with every point increase in VISA inflammatory score the odds of having severe disease increased by 1.77 times. Older age, male gender and diabetes were found to be significant on univariate analysis but became insignificant on multivariate analysis. Smoking was not found to be significant in both univariate and multivariate analyses. The lesser proportion of smokers on this cohort of patients might be a possible cause of this and needs to be evaluated further in a larger series of Indian population.

Conclusion

In conclusion, this study reports the clinical features of TED in an Indian cohort and the factors predictive of disease severity. Unlike Caucasian studies, there is no significant gender difference of TED in this cohort. The proportion of the patients with hypothyroid was higher compared to prior studies and most patients with hypothyroid had mild disease with dry eye symptoms the commonest presenting feature. Isolated lower eyelid retraction was seen in almost one-third of our patients and is similar to that reported from other studies from Southeast Asia. Hence, these findings can be included in the clinical criteria for diagnosis of TED. Hyperthyroidism and active disease were risk factors for severe and sight-threatening disease emphasizing the need for close follow-up and prompt detection and management of severe and sight-threatening disease especially in newly diagnosed hyperthyroid patients.

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Conflicts of interest

There are no conflicts of interest.

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