

Research Article

Factors Associated with Severe and Active Thyroid-Eye Disease in a Tertiary Hospital Setting

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Abstract

Purpose: The objective of this study is to determine risk factors and characteristics of TED in a tertiary hospital.

Methods: A 5-year cross-sectional study of patients diagnosed with TED from a highly specialized ophthalmology center in Manila, Philippines was done where demographics, medical history, family history, status of thyroid disease variables, and ophthalmologic exams were analyzed to identify associations with activity/severity of TED. Descriptive, univariate and multivariate analysis were used.

Results: Sixty-five patients were included: fourteen (21.5%) presented with active TED, while 28 (43.1%) had mild TED. No significant difference in terms of demographics found between active and inactive TED, and between severity groups. Active TED patients presented with prominent eyes (active TED 8: [57.2%], inactive TED: 13 [25.4%], p 0.0494), and eye pain (active TED: 3 [21.4%], inactive TED: 1 [2.0%], p 0.0289) more than inactive. Severe TED patients reported more prominent eyes over mild (severe TED: 17 [45.9%], p 0.0081, mild TED: 4 [14.3%]). No other variables were significant. Factors such as male sex, age, duration of thyroid disease, ATD use, Post-RAI, Post-thyroidectomy, comorbidities, pregnancy, family history of thyroid disease, smoking, TSH, and FT4 for were not significantly correlated with active/severe TED.

Conclusion: Risk factors and disease characteristics of TED cases at EAMC coincide with local published journals, except for significant correlation with male sex and TRAb titers showing the variability of the disease and the need for further studies.

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Keywords: Graves' disease; Graves' orbitopathy; Orbit; Thyroid; Thyroid Eye Disease; Thyroid-associated orbitopathy

Introduction

Thyroid Eye Disease (TED) is the most common cause of bilateral and unilateral proptosis in adults, with association of autoimmune thyroid disease such as Graves' disease and Hashimoto's thyroiditis, among others [1]. Autoantibodies which target thyroid tissue also target orbital tissues through receptors such as TSH-R and IGF1-R [2]. Often variable ophthalmologic signs and symptoms can precede signs of hyperthyroidism, indicating more threatening systemic disease [1,2]; Cases may present with manifestations in a regressed state of systemic involvement as well as hypothyroid and euthyroid states. In a Philippine study by Carlos-Rabocael al., most cases of thyroid disorders were found to be subclinical; thus, ophthalmologic signs and symptoms could be the only possible suggestions of a serious underlying thyroid disease [3].

The disease by itself may cause disabilities and discomfort from a range of complications which may further affect quality of life, where the experience of the disease has been described as "unpleasant, painful, cosmetically distressing and occasionally sight threatening; Daily mundane activities had also become unusually uncomfortable because of the symptoms [4]. During treatment, complaints about side effects of steroids such as weight gain and aggression were common. Even when active disease had abated, fibrosis and scarring of the orbital tissue can leave the patient only partially improved with regard to certain symptoms. Locally, there had been cases of patients that to leave work for several years [4].

With the burden, variability in presentation, and with the limited amount of data regarding the disease in the local setting, an inquiry into the characteristics of the local characteristics of the disease will be valuable in the management of TED.

The study aims to present the prevalence of TED in a tertiary hospital setting in the Philippines and investigate characteristics associated with severe and active TED.

Methods

The study is a cross-sectional study on patients diagnosed with TED from December 2013 to April 2018 at a tertiary health facility in Quezon City, Philippines. The study was granted technical and ethics approval by the East Avenue Medical Center's research ethics board. The authors had a sample size target of at least 58 patients to estimate an active TED rate of 8% and a moderate to severe TED rate of 8% [3]. This was computed with a margin of error of 7% and an alpha of 0.05.

Procedures and Measures

The search for patient records was done using the annual census of the ophthalmology department of a tertiary hospital. Once names and

identification numbers were tagged as having been diagnosed with TED, the medical records were retrieved. The diagnosis of TED was then verified based on the criteria for TED diagnosis by the American Academy of Ophthalmology [4].

Once a complete list of verified TED patients was compiled, the following data were recorded from the patient's records: sex, age, civil status, chief complaint, anti-thyroid drugs currently being taken at the time of visit, history of RAI, history of thyroidectomy, presence of co-morbidities, history of pregnancy, family history of thyroid disease, cigarette smoking history and status, laboratory level of thyroid stimulating hormone (TSH), and evidence of elevated Free Thyroxine (FT4). Smoking history was noted as either currently smoking, previous smoker (previous cessation prior to visit), or never smoked cigarettes [6].

The main outcomes of interest were TED activity and TED severity. Activity was assessed based on the Clinical Activity Score (CAS) system by Mourits et al (1989) [7]. Patients records were given one point for the presence of each of the following: spontaneous orbital pain, gaze evoked orbital pain, eyelid swelling that is considered to be due to active TED, eyelid erythema, conjunctival redness that is considered to be due to active TED, chemosis, and inflammation of caruncle or plica. A patient with 3 or more points out of 7 indicates active TED.

Severe and non-severe TED was based on the European Group of Graves' Orbitopathy (EUGOGO) classifications [8,9]. Non-severe TED followed the criteria for mild ophthalmopathy that was considered when the patient had one or more of the following signs: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos (<3 mm), transient or no diplopia, and corneal exposure responsive to lubricants. Severe TED on the other hand was composed of either moderate to severe TED and sight-threatening TED classifications. Moderate to severe ophthalmopathy was diagnosed when the patient presented with one or more of the following signs: lid retraction (>2 mm), moderate to severe tissue involvement, exophthalmos (≥3 mm), and with inconstant, or constant diplopia. If the patient was noted to have either ocular globe subluxation, severe forms of frozen eye, chorioidal folds, or postural visual darkening or if the patient presented with dysthyroid optic neuropathy or corneal breakdown due to severe exposure, the patient was considered to have sight-threatening ophthalmopathy. Lid retraction was based on margin reflex distance, using a millimeter ruler. Proptosis was measured using a Hertel exophthalmometer. Optic nerve involvement was determined to be present when there was a presence of relative afferent pupillary defect.

Explanatory variables on the outcome of interest were considered based on previous literature [3]. Explanatory variables included male sex, age, duration of thyroid disease, use of anti-thyroid drugs, previous RAI, previous thyroidectomy, presence of comorbidities, history of pregnancy, smoking history, TSH levels, and FT4 levels.

Statistical analysis

All data was encoded and prepared in Microsoft Excel 2019 and analysis was carried out using R 3.5.1. Descriptive statistics, including mean and median, are presented to describe the characteristics of the sample. Independent sample t-test was used for comparing continuous variables, and Fisher's exact test was used to compare the categorical variables between activity and severity groups. Logistic regression analysis was further used to analyze the association of different explanatory variables on the outcome of interest. A p value less than or equal to 0.05 was considered statistically significant.

Results

The initial search of the census revealed 65 patients diagnosed as TED. All the medical records tagged as TED were all found to contain all the necessary information for the study and were all verified as being a diagnosis of TED [10].

The mean age of TED patients was 39 (SD: 15.2) years old. There was a predominance of females (61.5%) and majority of the patients were either single (44.6%) or married (44.6%). The two most common primary complaint was prominent eyes (32.4%), followed by blurring of vision (15.4%). Median duration of thyroid disease was 36 (IQR: 26 - 52) months. There were 17 (26.2%) patients that were currently on ATD, two patients (3.1%) with history of RAI treatment, and two patients (3.1%) status post thyroidectomy. The median TSH level was 0.9 (IQR: 0.14 - 2.15) mIU/L, and the median FT4 was 11.9 (IQR: 6.86 - 16.28).

In terms TED activity, 14 patients (21.5%) were noted to have active TED, while 51 (78.5%) were classified as inactive TED. Table 1 presents the characteristics between activity groups.

Variables	Inactive (n=51)	Active (n=14)
Sex (male)	20 (39.2%)	5 (35.7%)
Age	39.3 + 16.4	37.7 + 10.1
Civil Status		
Single	22 (43.1%)	7 (50.0%)
Married	22 (43.1%)	7 (50.0%)
Widowed	3 (6.0%)	0 (0.0%)
Unspecified	4 (7.8%)	0 (0.0%)
Chief Complaint		
Prominent Eyes	13 (25.4%)	8 (57.2%)
Blurring of vision	10 (19.6%)	0 (0.0%)
Diplopia	6 (11.7%)	1 (7.1%)
Eye Swelling	6 (11.7%)	1 (7.1%)
Eye pain	1 (2.0%)	3 (21.5%)
Redness	4 (7.8%)	0 (0.0%)
Ptosis	1 (2.0%)	1 (7.1%)
Tearing	2 (3.8%)	0 (0.0%)
Duration of thyroid illness	55 + 48.1	54 + 79.4
Current ATD use	13 (25.4%)	4 (28.6%)
Methimazole	8 (15.7%)	3 (21.5%)
Propylthiouracil	4 (7.8%)	1 (7.1%)
Carbimazole	1 (2.0%)	0 (0.0%)
RAI	2 (3.8%)	0 (0.0%)
Thyroidectomy	2 (3.8%)	0 (0.0%)
Presence of comorbidities	15 (29.4%)	4 (28.6%)
History of pregnancy (n=40)	2 (6.5%)	0 (0.0%)
Family history of thyroid disease	10 (19.6%)	0 (0.0%)
Ever smoked	6 (11.7%)	2 (14.3%)
Currently smoking	6 (11.7%)	1 (7.1%)
Former smoker	0 (0.0%)	1 (7.1%)

TSH (mIU/L)	2.1 + 3.9	1.7 + 2.3
FT4 (ng/dL)	10.4 + 6.5	13.5 + 5.7

Table 1: Demographic and clinical characteristics of TED by activity.

Values are expressed as mean + SD and frequency (%)

Variables in bold are statistically significant at p<0.05

Active TED significantly had higher rates of chief complaints of prominent eyes (p= 0.0494) and eye pain (p= 0.0289) compared to inactive TED. There were no other statistically apparent difference between both groups. Logistic regression with explanatory variables defined a priori, correspondingly found no significant associations (Table 2).

Variables	OR	95% CI	p-value
Male sex	0.86	0.34 - 3.97	0.811
Age	0.99	0.95 - 1.03	0.732
Duration of thyroid disease	0.99	0.96 - 1.01	0.179
ATD use	1.16	0.23 - 3.20	0.816
Post RAI	*	*	*
Post thyroidectomy	*	*	*
Presence of comorbidities	0.96	0.28 - 3.85	0.951
History of Pregnancy	*	*	*
Family history of thyroid disease	*	*	*
Smoking History	1.25	0.14 - 4.48	0.799
TSH	1.04	0.87 - 1.23	0.693
FT4	1.04	0.93 - 1.16	0.507

Table 2: Bivariate logistic regression of factors associated with TED activity.

* Cannot be computed

In terms of severity, 28 (43.1%) patients were non-severe TED while 37 (56.9%) were noted to be severe TED. Significant difference was only found in the chief complaint of prominent eyes, which was more common in severe TED than non-severe TED (p=0.0081), (Table 3). Logistic regression again found no significant associations (Table 4).

Variables	Non-Severe (n=28)	Severe (n=37)
Sex (male)	12 (42.9%)	13 (35.1%)
Age	37.4 + 15.1	40.1 + 15.4
Civil Status		
Single	11 (39.3%)	18 (48.6%)
Married	10 (35.7%)	19 (51.4%)
Widowed	3 (10.7%)	0 (0.0%)
Unspecified	4 (14.3)	0 (0.0%)
Chief Complaint		
Prominent Eyes	4 (14.3%)	17 (46.0%)
Blurring of vision	6 (21.2%)	4 (10.8%)
Diplopia	4 (14.3%)	3 (8.1%)
Eye Swelling	2 (7.1%)	5 (13.5%)
Eye pain	1 (3.6%)	3 (8.1%)

Redness	2 (7.1%)	2 (5.4%)
Ptosis	1 (3.6%)	1 (2.7%)
Tearing	1 (3.6%)	1 (2.7%)
Duration of thyroid illness	72 + 75.4	41 + 25.0
Bilateral	12 (42.8%)	13 (35.1%)
Current ATD use	8 (28.6%)	9 (24.3%)
Methimazole	7 (25.0%)	4 (10.8%)
Propylthiouracil	1 (3.6%)	4 (10.8%)
Carbimazole	0 (0.0%)	1 (2.7%)
RAI	1 (3.6%)	1 (2.7%)
Thyroidectomy	1 (3.6%)	1 (2.7%)
Presence of comorbidities	7 (25.0%)	12 (32.4%)
History of pregnancy (n=40)	1 (6.25%)	1 (4.2%)
Family history of thyroid disease	6 (21.2%)	4 (10.8%)
Ever smoked	2 (7.1%)	6 (16.2%)
Currently smoking	2 (7.1%)	5 (13.5%)
Former smoker	0 (0.0%)	1 (2.7%)
TSH (mIU/L)	1.8 + 2.6	2.1 + 4.0
FT4 (ng/dL)	10.8 + 6.0	11.6 + 6.7

Table 3: Demographic and clinical characteristics of TED by severity.

Values are expressed as mean + SD and frequency (%)

Variables in bold are statistically significant at p<0.05

Variables	OR	95% CI	p-value
Male	1.39	0.26-1.98	0.526
Age	1.01	0.98-1.05	0.474
Duration of thyroid disease	0.99	0.97-1.00	0.11
ATD use	1.25	0.26-2.44	0.7
Post RAI	1.33	0.04-12.54	0.841
Post thyroidectomy	1.33	0.04-12.54	0.841
Presence of comorbidities	0.69	0.48-4.32	0.514
History of Pregnancy	1.54	0.04-11.24	0.767
Family history of thyroid disease	2.27	0.11-1.76	0.24
Smoking History	0.4	0.47-13.54	0.27
TSH	1.06	0.83-1.34	0.644
FT4	1.01	0.92-1.12	0.773

Table 4: Bivariate logistic regression of factors associated with TED severity.

Discussion

This study done in a tertiary hospital in Quezon City, Philippines, examined characteristics of all Thyroid Eye disease patients that had consulted for a span of 5 years. The review of records showed that most of the cases were female (61.5%) both locally (86.20% [1] and 81% [3]) and in the rest of Southeast Asia (63.8%) [11], showing similar female predominance of the disease. The mean age was found to be 39 years. By regional geography, there was a similarity with the aforementioned demographics of our study population.

Disease activity was also found to have similar findings in the region. There was an overall predominance of inactive disease at 78.5% of the total study population. Albeit our study predominance was

lower, this lower proportion was also found in other local (98%) [3] and international data (89.1%) [11].

Severity on the other hand had different findings where patients with moderate to severe disease comprised slightly more than half of the study population (56.92%). This result was surprising with our chart review since not only were the severe cases not a minority but rather slightly of bigger proportion of the cases in our center. Published articles showed a minority of severe disease locally (8%) [3] and internationally (8%) [11] in their study population. Furthermore, females dominate the proportion of severe cases in our study, another finding which is peculiar. It is a known fact that the male gender is a risk factor for more severe cases [4]. Possible reasons why this will be discussed below.

The data presented could have been affected by certain locality factors. Our hospital was highly accessible by public transport within the city and was with nearly no consultation fees for the healthcare at the tertiary level. This may have a role with the results correlating well with the fact that the younger age group is more mobile, where they can easily seek for consult. Though accessibility shows some agreement with the predominance of inactive disease and a younger population, this was not the case with the comparable number of mild and moderate-severe disease groups. This could have some relevance with the reflection of general poor health seeking behavior in the Philippines, where medical expertise is only sought with perception of actual illness, i.e., when symptoms are bothersome or more evident. Some examples of obvious disease may be when more severe disease already affects daily activity, quoted by local authors as a “crisis oriented attitude towards health [12].” There are other forces that come into play with the general state of health in the country such as health systems, community, family and other personal issues [13] that heavily influence health behavior out of the scope of this study.

Another reason for the increased proportion of moderate-severe TED cases was the lack of a standard of procedure for the outpatient department of our hospital. On consult with the endocrinology department, it was found that only the thyroid disease patients with obvious signs of TED were referred to the center. Only until recent guidelines were all cases of thyroid disease referred for TED screening. Even then, not all patients did proceed with the referral probably because of the aforementioned poor seeking behavior.

Based on our findings, bilateral TED (38.45%) occurred much less than unilateral TED (61.5%). The known classical presentation of TED is bilateral which also occurs more commonly [14], thus making this study finding peculiar. The authors think that this could be due to the fact that most TED cases at our center are diagnosed clinically due to financial constraints and overall health system of the Philippines. It is known that the disease is prevalently asymmetric in presentation [15], thus the contralateral side may look more normal than the more severe side making an error in diagnosis is likely. With current improvements and more access to better imaging, this may be rectified in the future.

In relation to TED activity, there was significant correlation with presenting symptoms of prominence of eyes and eye pain. This finding corresponds well with the pathophysiology of activity where inflammation can cause orbital tissue to be inflamed causing mechanical protrusion of eyes as well as tightness of tissues causing pain. Acute TED would be more noticeable for patients since the active state can cause a rapid change in appearance making patients seek

consult. Compared to other studies, this finding was different since lid retraction was a consistent chief complaint [1,16]. This may be due to the fact that bulging eyes may be more obvious than a retracted eyelid which may be thought of as more urgent to patients. Similarly, severity was only positively correlated with prominence of eyes as the presenting symptom most probably due to similar reasons, where in this symptom is more obvious when disease is more severe. Other common presenting signs with our cases included blurring of vision, diplopia, and eye swelling though these were not significant.

This study was done in the national referral center for eye care where patients include referrals from across the nation. All TED patients over 5 years were included, where specialists have seen and handled these cases. Since most cases were primarily seen by our department, there might be a lack of data from primarily Thyroid Disease patients from the Endocrinology service. Better standards of procedure are currently being established for more holistic care for these patients [17].

To conclude, TED in our local setting had been described to be similar in terms of mean age, female predominance and more frequent presentation in the inactive state. Due to some local factors though, moderate-severe disease was found to occur more frequently than other published studies. For our population, there was no significant risk factor with regard to severity showing much variability with the disease in our local setting, thus there is a need to look into the characteristics of this disease more.

Author's Disclosure

The authors declared no conflict of interest or any funding whatsoever.

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