



Original research

The epidemiological characteristics of patients with thyroid eye disease in a referral center in northern Iran

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Received 7 March 2018; revised 19 June 2018; accepted 2 July 2018

Available online 19 July 2018

Abstract

Purpose: This study was conducted to determine the demographics, clinical features, severity, and activity of thyroid eye disease (TED) in patients of a referral center in the north of Iran.

Methods: Patients with TED who were referred to Amir-almomenin Hospital, Rasht, Iran from March 2012 to March 2014 were enrolled in this cross-sectional study. The measurements of proptosis, lid width, lagophthalmos, extraocular muscle function, and visual acuity were recorded. The activity of ophthalmopathy was scored according to the clinical activity score (CAS).

Results: TED was diagnosed in 103 patients with a mean age of 42.1 ± 13.91 years. Of those patients, 52.4% were women, and 80% had hyperthyroidism. The mean duration of TED was 36.5 ± 53.12 months. Extraocular muscle involvement (98%) and eyelid retraction (88.3%) were the most common manifestations. Per the CAS results, 86 (83.5%) patients were at stage 0, and there was a significant difference in CAS scores between male and female patients, $P = 0.02$.

Conclusions: The characteristics of TED in patients of the studied referral center during a two-year period, including common signs and symptoms, disease duration, treatment, an activity of disease were determined. Notably, many patients in this study had orbital squel of TED meaning that they had inactive TED. Proper management of this serious complication requires close cooperation between endocrinologists and ophthalmologists to ensure timely referrals for appropriate care.

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Keywords: Eye manifestations; Thyroid eye disease; Epidemiological characteristics

Introduction

Thyroid diseases can cause several complications and comorbidities outside the thyroid.¹ One important complication, especially for those with hyperthyroidism and Grave's disease, is ophthalmopathy, known as thyroid eye disease (TED). Although its precise pathology is uncertain, ophthalmopathy is thought to be an autoimmune disorder related to the production of the IgG antibody, which is associated with other autoimmune diseases, such as myasthenia gravis, Addison's disease, and vitiligo.^{2,3} The pathogenesis of most

signs and symptoms of TED is associated with increased volume inside a limited bony space that results from inflammatory cytokines, which cause proptosis, or extraocular muscle involvement.⁴ Therefore, it is essential to appropriately diagnose and treat patients with TED. Notably, it seems that a combination of endogenous, genetic, and environmental factors play a key role in its incidence and severity.⁵

Several classifications have been developed to identify both the activity and severity of TED to appropriately manage it. The initial classifications developed included Werner's no signs and symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle involvement, corneal involvement, and sight loss (known as NO SPECS),⁶ which has several limitations that reduce its predictive value; hence, it is not currently used regularly.

Conflict of interest: The authors have no conflict of interest to declare.

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Peer review under responsibility of the Iranian Society of Ophthalmology.

The activity of ophthalmopathy is scored according to the clinical activity score (CAS) (developed by Mouritis and colleagues), which shows a 65% positive predictive value for response to radiotherapy.⁷ The Rundle score classifies TED severity into four groups.⁸ Recent classifications include vision, inflammation, strabismus, and appearance (known as VISA)⁹ and the European Group of Graves' Orbitopathy (EUGOGO) classifications.^{10,11}

The prevalence and characteristics of TED have been investigated in several populations, such as those of Denmark¹² and Sweden¹³; however, scarce data exists regarding the prevalence of TED in the Iranian population.¹⁴ Iranian studies have either only evaluated a small sample size or have not thoroughly investigated all signs and symptoms.^{15,16} Because of the variations caused by differences in ethnicity and geographical area on the incidence and characteristics of TED, insufficient evidence on characteristics of TED in the Iranian population, as well as no available studies on this issue in the Guilan province, the present study aimed to determine demographics, clinical features, severity, and activity of TED in the patients of a referral center in northern Iran.

Methods

In this cross-sectional study, all medical files of patients diagnosed with TED who were referred to Amir-almomenin Hospital, Rasht, Iran from March 2012 to March 2014 were studied. This hospital is a specialized referral medical center for eye diseases in Guilan province. The protocol of the study was approved by the Ethics Committee of Guilan University of Medical Sciences. Before recruitment, the study's design and objectives were explained to the patients, and written informed consent was obtained. Principles of the Declaration of Helsinki were met throughout each step of the study. All patients' information was kept confidential, used only for the purposes of the research, and analyzed anonymously. We included all patients with a diagnosis of TED based on clinical, paraclinical [magnetic resonance imaging (MRI), computed tomography (CT) scanning, and visual field (VF) analysis], and laboratory findings (free T4, T3, TSH, thyroid autoantibodies). For this study, a checklist was designed to collect the necessary information, including demographic information [sex, age, weight, and height for calculation of body mass index (BMI)], any history of smoking, medical and family history of thyroid diseases, clinical complaints of the patient at the first visit, and complete eye examinations, all of which were extracted from the hospital's medical records. Eye examinations included measurement of proptosis, lid width, lagophthalmos, eye muscle function, and visual acuity. The Snellen chart measured visual acuity, and intraocular pressure (IOP) was measured via an applanation tonometer. A ruler measured eyelid abnormalities as millimeters of visible sclera both below and above the central corneal limbus with the head and eye in the neutral position and as millimeters of closure deficiency (lagophthalmos). Eye proptosis was recorded using Hertel exophthalmometry (with a value of ≥ 20 mm as a cut-off point). Signs of orbital inflammation were recorded using

a 0–4 score (0: none; 1: mild redness and swelling; 2: moderate redness and swelling; 3: considerable redness and swelling with chemosis; 4: severe chemosis, swelling, and redness). All of the measurements were performed by an expert ophthalmologist (A.R.M.).

The activity of the ophthalmopathy was scored according to the CAS, which consists of clinical items of inflammation that can be determined easily at clinics. The CAS is also based on having 4 classical signs of inflammation, which are scored from 0 to 10. These 4 factors are pain (2 scored), redness (2), swelling (4), and impaired function (2).⁷ The CAS has a high predictive value for the outcome of immunosuppressive treatment in Graves' ophthalmopathy.⁷

Statistical analysis

After data collection, the data were entered into SPSS (Version 21.0. Armonk, NY: IBM Corp.). All studied variables were firstly examined for normal distribution using the Kolmogorov normality test. If the data followed normal distribution, parametric tests, such as the *t*-test, were performed. Otherwise, non-parametric tests were used for comparison of numeric variables, while categorical variables were compared using the chi-square test. For better comparison of frequencies among different ages, age was categorized into 4 groups (16–30, 31–45, 46–60, and >60 years). Descriptive results were reported by frequency (percentage) and mean \pm standard deviation (SD). The significance level of the tests was set at 0.05.

Results

Demographic data

During the study period, 103 patients were evaluated. The mean \pm SD age of the participants was 42.1 ± 13.91 (range, 19–83) years, with 39.8% in the age category of 31–45 years. In total, 52.4% of the participants were women with a mean \pm SD age of 40 ± 12.6 years, and 49 (47.6%) patients were men with a mean \pm SD age of 45 ± 12.57 years ($P = 0.4$). Comparing the prevalence of TED among four age categories showed no statistically significant difference ($P = 0.06$) (Table 1).

The mean BMI of the study population was 29.9 ± 22.06 kg/m², with many patients' (41%) BMIs placing them in the category of overweight. There was no significant difference in BMI between men and women

Table 1
Frequency of the thyroid eye disease (TED) according to sex and age group.

Age group	Total	Male	Female	<i>P</i> -value
16–30	23 (22.3%)	7 (14.2%)	16 (29.6%)	$P = 0.06$
30–45	41 (39.8%)	21 (42.8%)	20 (37%)	
45–60	29 (28.1%)	13 (26.5%)	16 (29.6%)	
>60	10 (9.7%)	8 (16.3%)	2 (3.7%)	
Total	103 (100%)	49 (47.5%)	54 (52.4%)	

(30.53 ± 31.5 vs. 28.93 ± 5.7 kg/m², respectively, *P* = 0.2). Seventy-three patients (70.8%) did not mention a history of smoking, and only 19 patients (18.4%) were current smokers at their first visit. Ninety-five patients (92.23%) did not mention any history of skin disease, and 72 patients (70%) did not mention any concomitant diseases, while 13% noted the presence of diabetes, 4% myasthenia gravis, and 11% cardiovascular diseases. Seventy-five (72.7%) patients did not mention any family history of either thyroid disease or TED.

Thyroid status

Most patients (83.80%) had hyperthyroidism. In addition, 1 (0.9%) patient was euthyroid (normal thyroid gland function), and 19 (18.44%) had hypothyroidism. There were no significant differences in sex, age, and BMI between patients with hyperthyroidism and hypothyroidism (*P* > 0.05). The mean duration of thyroid disease in patients with TED was 69.04 ± 80.3 (range, 3–480) months.

Systemic and ocular manifestations

The most common clinical complaints of patients at diagnosis of TED were weight loss (35.9%), proptosis (31.1%), and cardiac palpitation (10.7%), with a statistically significant difference in the frequency of clinical complaints between men and women (*P* = 0.03). The most common complaint in men was eye proptosis (42.9%), while in women it was weight loss (37%). The clinical symptoms are compared between the left and right eye in Table 2.

The mean duration of clinical eye complaints in the patients was 36.5 ± 53.12 (range, 0–240) months, with no statistically significant difference between both male and female patients (29.95 ± 45.8 vs. 42.77 ± 57.34 months, respectively, *P* = 0.1) or patients with hyperthyroidism and hypothyroidism (34.26 ± 50.84 and 48.05 ± 59.5 months, respectively, *P* = 0.06). Most patients (60%) had a visual acuity of 10/10, and the remaining patients had a visual acuity of 2/10 to 9/10. All patients had normal color vision and Marcus-gun was

Table 3
Categorization of positive clinical signs at physical examination.

Categorization of the clinical sign		Right eye	Left eye
Types of corneal infiltration	1/3 Upper	0	0
	Central	3 (2.9%)	4 (3.9%)
	1/3 lower	19 (18.4%)	15 (14.6%)
	No ulcer	81 (78.7%)	84 (81.5%)
Eye movement limitation	In all directions	60 (58.2%)	60 (58.2%)
	Outside	8 (8.7%)	18 (17.5%)
	Inside	20 (19.4%)	12 (11.7%)
	Upward	9 (8.8%)	8 (7.8%)
	Downward	0	2 (1.9%)
	Up and inside	3 (2.9%)	0
	Down and inside	0	0
	Up and outside	1 (1%)	0
	Down and outside	0	1 (1%)
	Unlimited	2 (1.9%)	2 (1.9%)

negative in all patients. The cup-to-disk ratio was 0.2 in most patients. The IOP increased in 16 (15.5%) patients. The mean upward-gaze IOP in the right eye was 20.94 ± 6.25 mmHg (range, 10–45). In the left eye, it was 19.4 ± 4.88 mmHg (range, 10–36). The primary position of the IOP in the right eye and the left eye was 17.9 ± 3.6 (range, 10–36) and 17.07 ± 3.24 (range, 10–28) mmHg, respectively. The difference in IOP in up and primary positions was more than 6 mmHg in 8 (7.7%) patients in the right eye, in 3 (2.9%) patients in the left eye, and in 18 (17.47%) patients in both eyes. The frequency of clinical signs is demonstrated, per the affected eye, in Table 2.

The most common findings in clinical examinations were eye movement limitation in 101 (98%) patients, eyelid retraction in 91 patients (88.3%), and proptosis in 57 patients (55.33%), which were bilateral in 96.1%, 31.1%, and 33%, respectively. Corneal infiltrations were found on examination in only 19 (18.4%) patients in the right eye and in 15 (14.6%) patients in the left eye. Other positive findings from the eye examinations are demonstrated in Table 3.

The interval between the diagnosis of thyroid disease and TED was <18 months in 66% of patients, 19–60 months in <20%, and >60 months in 14%, with no difference between male and female patients (*P* = 0.75).

Table 2
Frequency of eye examination results in patients with thyroid eye disease (TED) at their first visit according to the affected eye.

Eye examination results		Right eye	Left eye	Both eyes	None of them
Positive signs in clinical examination	Proptosis	14 (13.6%)	9 (8.7%)	34 (33%)	46 (44.7%)
	Eyelid retraction	54 (53%)	5 (4.9%)	32 (31.1%)	12 (11.7%)
	Lid lag	7 (6.8%)	9 (7.8%)	29 (28.2%)	58 (56.3%)
	Chemosis	3 (2.9%)	0	2 (1.9%)	98 (95.1%)
	Increased IOP	7 (6.8%)	4 (3.9%)	5 (4.9%)	87 (84.5%)
	Puffy eyes	4 (3.9%)	0	50 (48.5%)	49 (47.6%)
	Localized redness	0	1 (1%)	2 (1.9%)	100 (97.1%)
	General redness	3 (2.9%)	0	10 (9.7%)	90 (87.4%)
	Periorbital edema	0	2 (9.1%)	1 (1%)	100 (97.1%)
	Eye movement limitations	1 (1%)	1 (1%)	99 (96.1%)	2 (1.9%)
	Corneal infiltration	1 (1%)	2 (1.9%)	17 (16.5%)	83 (80.6%)
	Diplopia	—	—	11 (10.7%)	92 (89.3%)

IOP: Intraocular pressure.

Thyroid treatment states

At the first visit, 53.2% (55 patients) of the participants were using the anti-thyroid drug methimazole, 39.8% (41 patients) were using levothyroxine, and 6.8% (7 patients) were not being treated. The most commonly prescribed treatment was methimazole (70.8%), while 22% used radioactive iodine, 4% underwent surgery, 1% used combinational therapy, and 2% remained untreated.

Disease activity scores

We evaluated the activity of disease per the CAS systems. Most patients had a stage 0 of CAS, and there was a significant difference in CAS scores between male and female patients: women > men, $P = 0.02$ (Table 4). The mean CAS in hyperthyroid patients was less than in hypothyroid patients (0.26 ± 0.69 vs. 0.57 ± 1.0 , respectively, $P = 0.04$).

Discussion

Demographic status

To the best of our knowledge, for the first time, the present study determined the frequency of common symptoms and signs of TED in an Iranian population that had been referred to an eye center in northern Iran. Among the 103 patients with TED with a mean age of 42.1 ± 13.91 years (mainly in the age category of 30–45 years), which consisted of 52.4% women, most (80%) had hyperthyroidism.

In developed countries, the natural course and characteristics of TED have not been completely defined, especially in the advanced stages, because they are often appropriately diagnosed and treated in the early stages.¹⁷ In developing countries, including Iran, a pressing issue is the appropriate diagnosis of suspected cases of TED by endocrinologists and timely referral of those patients to an ophthalmologist to receive treatment as early as possible. Notably, data published from developed countries provide the results of national data registry systems that report long-term results. For instance, Danish studies that reported the incidence and characteristics of TED during a 20-year period described a female-to-male ratio of nearly 5,^{12,18} which has been similarly reported in other studies.¹⁹ Conversely, in the present study, the percentage of female and male patients were almost similar, which

was consistent with a previous study in the Iranian population that reported a female-to-male ratio of nearly 1 and a ratio of 0.72 in patients with restrictive myopathy. These statistics suggest different incidence rates in female and male patients, per disease severity.¹⁶ Additionally, other researchers have reported similar incidences between male and female patients.²⁰ The difference among the female-to-male ratio of our study and the previous Danish studies could be due to the differences in study design. The present study was a cross-sectional study with a small sample size, while the Danish study included nationwide cohort studies. Furthermore, the incidence of TED was approximately similar in male and female patients in severe cases, and differences in disease characteristics of the studied population can affect these statistics.

Disease activity states

Per the CAS, most patients (83.5%) were at stage 0. The activity of TED was similar between patients with either hyper or hypothyroidism in the present study, which paralleled the results of previous research.²¹ It has been found that the severity and activity of TED are often dissimilar among different populations. For example, an investigation of 346 patients that classified patients according to EUGOGO reported no TED in 73.7%, mild and inactive TED in 20.2%, and moderate-to-severe and active TED in 5.8%.¹⁷ These differences, in addition to the differences in characteristics of the studied population, can be due to the different criteria used to classify the severity and activity of TED. This finding emphasizes the silent nature (stable phase) of TED in our studied population.

Ocular manifestations states

The results of the present study also indicated extraocular muscle involvement (98%) and eyelid retraction (88.3%) as the most common manifestations and weight loss (35.9%) and proptosis (31.1%) as the most common clinical complaints. An Iranian study reported proptosis (63.4%), soft tissue involvement (40.9%), and extraocular muscle involvement (22.1%) as the most common signs among 303 patients with TED,¹⁴ while other reports have concluded that lid retraction was the most common finding.^{15,22} These differ from the results of the present study regarding the most common finding, including the reported percentages. In addition, the frequency of extraocular muscle involvement in the current study appears higher than in these studies as well as in another previous Iranian study, which reported that finding in less than half its patients.¹⁶ Similar to the results of the present study, an investigation of 120 patients with TED indicated eyelid retraction (91%), proptosis (62%), and extraocular muscle dysfunction (42%) as the most common ocular findings.²³ The variations in signs and symptoms of TED can be justified by different characteristics of the disease in the study population, such as severity and activity. Many of the patients in our study had orbital sequelae of TED (restrictive myopathy, lid retraction,

Table 4
Frequency of clinical activity score (CAS) in patients with thyroid eye disease (TED) according to sex.

Clinical activity score (CAS)	Total	Male patients	Female patients	P-value
0	86 (83.5%)	35 (71%)	51 (94%)	0.02
1	8 (7.8%)	6 (12%)	2 (3%)	
2	4 (3.9%)	3 (6%)	1 (1%)	
3	3 (2.9%)	3 (6%)	0	
4 And higher	2 (1.9%)	2 (4%)	0	
Total	103 (100%)	49 (47.6%)	54 (52.4%)	

The result of chi-square test are reported at significance level of 0.05.

proptosis, etc.). In other words, these patients had inactive but moderate-to-severe TED. These sequelae caused the patients to seek medical care. As demonstrated in the present study, the frequency of signs and symptoms differed between patients with hypothyroidism vs. hyperthyroidism, and approximately 80% in the present study had hyperthyroidism. Lid retraction has been reported to have a causative relationship with proptosis.²⁴ Therefore, it is suggested as an important sign to consider in patients with thyroid dysfunction for appropriate and on-time referral of patients to an ophthalmologist. Furthermore, extraocular muscle involvement is an important finding that can determine proper disease management and treatment protocols.²⁵

Nevertheless, as described above, many different signs were detected during eye exams by an ophthalmologist. Previous studies have reported ophthalmic symptoms, such as pain and discomfort, dryness, photophobia, diplopia, and blurred vision with TED.^{23,26} The frequency of these particular symptoms was quite low in the present study. This finding emphasizes that many of the patients in this study had orbital sequelae of TED, and this reality supports the idea that early and significant clinical investigation of suspected TED by an endocrinologist as well as and more attention to TED signs during regular visits are necessary.

Thyroid treatment states

Per the results of the present study, the most commonly prescribed treatment was methimazole (70.8%), while 22% of patients were treated with radioactive iodine, 4% underwent surgery, 1% used combinational therapy, and 2% remained untreated. These statistics are close to that of Reddy and colleagues, who reported 95%, 2%, and 3%, respectively.²⁰ Treatment of TED can be selected from among a wide range of modalities and is generally based on disease severity and activity, which predict treatment response.²⁷ Choosing the proper treatment is important because a significant proportion of TED signs and symptoms often remain after treatment, causing patient dissatisfaction.²⁸ This motivates researchers to seek alternative treatments and makes it challenging to clinically manage orbitopathy.²⁹

The present study was the first to determine the frequency of all signs and symptoms associated with TED as well as other characteristics, such as disease severity, duration, and treatments, in a northern Iranian population. However, some of the results vary significantly from those of previous studies. The difference appears to be due to selection bias; only severe cases were referred to this tertiary center. For example, the most common finding in the present study was eye movement limitation, which can only be seen in severe cases, and many of the patients in this study had restrictive myopathy. In other words, these patients had inactive but moderate-to-severe TED. Other limitations of the present study were its cross-sectional nature and lack of follow-up. Furthermore, the data were extracted from the medical records of patients, and any errors in those records could have affected the results of the present study. In addition, most variables were defined

clinically. A multicenter cohort study with a larger sample size would better clarify these demographic characteristics.

In conclusion, the results of the present study determined the primary characteristics of TED in patients at a referral center during a two year period, including the incidence of signs and symptoms, disease duration, treatment and activity of disease, and it emphasized that TED is a significant health concern among patients with thyroid disorders. Proper management of this serious complication requires close cooperation between endocrinologists and ophthalmologists to ensure the timely referral of patients for appropriate treatment.

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