ORIGINAL ARTICLE

Correlation of TED Laterality with Thyroid Status among Thyroid Eye Disease (TED) Patients in a Tertiary Hospital in Indonesia

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ABSTRACT

Introduction: Thyroid eye disease (TED), an autoimmune thyroid disorder, is prevalent in Asian countries and exhibits a variety of manifestations. Orbital involvement in TED is usually bilateral but may occur unilaterally in some cases. While it is commonly associated with hyperthyroidism, it also manifests in individuals with hypothyroidism or euthyroidism. The purpose of this study was to investigate the relationship between TED laterality and thyroid status in TED patients treated at the Eye Oncology Clinic of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia.
Methods: The study was retrospective, analytical and observational. Patients diagnosed with TED who were treated at Dr. Soetomo General Academic Hospital between January 2019 and December 2021 were the focus of this study. SPSS analyses of medical records that satisfied the sample criteria were used to compile the data for this study.
Results: There were 88 samples that were dominated by females (57.95%) and aged 41 – 50 (32.96%). Proptosis was the most common clinical manifestation (94.32%), with compressive optic neuropathy was the least common (3,41%). Eyelid retraction occurred in only 22.7% of the patients. TED was categorized into unilateral (44.32%) and bilateral (50%). The majority had hyperthyroidism (70.45%), followed by euthyroidism (25%), and hypothyroidism (4.55%). It was found that there was a significant correlation between thyroid status and TED laterality. Compared to euthyroidism, abnormal thyroid conditions such as hyperthyroidism and hypothyroidism develop bilateral TED more frequently than normal thyroid conditions.
Conclusion: There was a correlation between TED laterality and thyroid status among patient TED.

Keywords: Thyroid Eye Disease; TED laterality; thyroid status; clinical features; disease

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INTRODUCTION

Thyroid eye disease (TED) is an extrathyroidal type of autoimmune thyroid disease that produces inflammation and complex orbital inflammation and remodelling. Orbital and periorbital tissues are damaged by TED (Hasibuan et al., 2018; Das et al., 2022). Despite the fact that this condition is believed to be a normal self-limiting autoimmune syndrome, it is possible for it to result in a loss of vision, a decline in quality of life, and functional issues that lead to discomfort (Soebagjo, 2015).

Chin et al. (2020) found an increase in reported cases of TED in studies conducted after 2010 compared to those before 2010. Additionally, data indicate that Asian countries have a higher incidence of TED (44%) compared to Europe and America. The fact that Asians are more susceptible to TED (45%) is also supported by several previous studies (reference). It is standard practise to correlate TED with Graves' hyperthyroidism since the majority of people who have TED also have the biochemical indications of hyperthyroidism. A systematic review by Muñoz-Ortiz (2020) revealed a global incidence rate for TED, with 10.36% in hypothyroidism, 86.2% in hyperthyroidism, and 7.9% in euthyroidism. Although the highest prevalence is linked to hyperthyroidism, the disease can also be found in patients with clinical hypothyroid or euthyroid status (Mcalinden, 2014; Weiler, 2017).

TED will often have an equal impact on both orbits, although there are some people who may have asymmetrical orbital involvement. When just one eye is affected by clinical signs of TED, such as inflammation, proptosis, eyelid retraction, diplopia, and compressive optic neuropathy, the symptoms are said to be unilateral.

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This is because the opposite eye does not exhibit any symptoms (Eshraghi et al., 2023). Conversely, TED is classified as bilateral when characteristic orbital signs and radiographic findings point to both eyes. Eshraghi et al. (2023) also stated that bilateral clinical presentations are more commonly found than unilateral ones in TED, and unilateral cases can evolve into bilateral forms over time. Continuous unilateral involvement can occur. Although this is not always the case, there is evidence to suggest that a disease that at first seems to be affecting just one side may really affect both sides (Kashkouli et al., 2011). This study aimed to provide information about TED patient profiles based on sex, age, clinical features, TED laterality, thyroid status, and the correlation between the laterality of TED patients with their thyroid status.

METHODS

This particular study was a retrospective analytical observational study. The patients who were diagnosed with TED and attended appointments at the Outpatient Oncology Eye Clinic located at the Dr. Soetomo General Academic Hospital, a tertiary hospital in Surabaya, Indonesia from January 2019 to December 2021 made up the study population. The major source of data for this study came from the medical records of TED patients treated at the hospital. These patients had to meet certain criteria in order to be included in the sample frame. The inclusion criteria for this study included medical records containing clinical descriptions of the patients and thyroid status laboratory results, while exclusion criteria involved patients with other eye conditions. The data was then analyzed using IBM SPSS Statistics. The research protocol for this study had received ethical approval and certification from the Research Ethics Committee of Dr. Soetomo General Academic Hospital with reference number 107/LOE/301.4.2/X/2022.

RESULTS

At Dr. Soetomo General Academic Hospital, 138 individuals were diagnosed with TED between the years 2019 and 2021. However, only 88 samples of those patients' medical records met the inclusion criteria for this research. The characteristics of the patients in this study were described based on gender, age group, clinical profile, TED laterality, and thyroid status. The frequency and percentage of the subjects' characteristics are presented in Table 1.

In all, there were 51 female participants in this study, making up 57.95% of the total population. Patients under the age of 10 made up the smallest percentage of the total, while patients aged 41 to 50 made up the largest percentage (32.96% of the total). Proptosis was the most often symptom reported by the physicians (94.32%), while compressive optic neuropathy was the least (3.41%). Regarding thyroid status, the majority of TED patients had hyperthyroidism (70.45%), followed by euthyroid (25%), and lastly, hypothyroid (4.55%).

In Table 2 Fisher's exact test results show that the laterality of TED with thyroid status has a significant association with TED occurrence (p=0.002). Therefore, further analysis was conducted to determine the differences between unilateral and bilateral TED for each thyroid status. All the differences indicated between TED laterality and thyroid status were analyzed using logistic regression, as presented in Table 3. When hypothyroidism was compared to euthyroidism, a significant difference was observed (p=0.014). The likelihood of this difference can be seen by examining the Odds Ratio (OR). An OR=3.667 means that patients with hypothyroidism have a 3.6 times higher incidence of bilateral TED compared to euthyroidism. Additionally, when hyperthyroidism was compared to euthyroidism, there was a significant difference (p=0.006) with an OR of 4.222, meaning that hyperthyroid patients are 4.2 times higher incidence of bilateral TED compared to euthyroidism. However, when hyperthyroidism was compared to hypothyroidism, there was no significant correlation between that groups. (p=0.288, p>0.05).

Table 1. Characteristics of TED Patients

Variable	n (%)
Sex	
Male	37 (42.0)
Female	51 (58.0)
Age (years)	
<10	1 (1.1)
10-20	4 (4.6)
21-30	18 (20.5)
31-40	14 (15.9)
41-50	29 (33.0)
51-60	18 (20.5)
61-70	4 (4.6)
Clinical Features	
Proptosis	83 (94.3)
Eyelid erythema and swelling	53 (60.2)
Eyelid retraction	20 (22.7)
Chemosis and caruncle edema	11 (12.5)
Restrictive strabismus	10 (11.4)
Compressive optic neuropathy	3 (3.4)
TED Laterality	
Unilateral	40 (45.5)
Bilateral	48 (54.6)
Thyroid Status	
Hypothyroid	4 (4.6)
Euthyroid	22 (25.0)
Hyperthyroid	62 (70.5)

Table 2. Correlation between TED laterality and thyroid status

TED Laterality	Thyroid Status			p-value
	Hypothyroid	Euthyroid	Hyperthyroid	
Unilateral	0 (0%)	16 (18%)	24 (27%)	0.002*
Bilateral	4 (5%)	6 (7%)	38 (43%)	

*correlation is significant

Table 3. Comparison of TED laterality and thyroid status

Comparison	OR (95% CI)	p-value
Euthyroid-Hypothyroid	3.667 (1.853-7.255)#	0.014b*
Euthyroid-Hyperthyroid	4.222 (1.451-12.290)	0.006a*
Hypothyroid-Hyperthyroid	1.632 (1.339-1.988)#	0.288b

aChi-square Test
bFisher's exact Test
#Only for bilateral proptosis group
*Differemce is significant

DISCUSSION

This study found that the majority of the respondents were female. This was consistent with the research conducted by Lim S.L et al. (2008a) in a multi-ethnic Malaysian population, where the study found that TED cases in women were 1.5 times more common than in men. A recent study conducted in Iran reported 55.6% women, in Greece 51.5%, while in the USA, it was reported that 77% of TED patients were women (Eshraghi et al., 2023; Ho et al., 2023; Tsiogka et al., 2023). According to the studies, more TED cases occurred in women because women had a higher risk of autoimmune

diseases compared to men (Shah and Patel, 2023).

The age distribution of TED patients at Dr. Soetomo General Academic Hospital, Surabaya, during the period 2019 to 2021 was highest in the 41-50 age group. This finding aligned with the results of Restiadi (1994) conducted at the same location 30 years ago. Boesoirie et al. (2012) also found the highest age distribution in the 41-50 age range in their research at Cicendo Eye Hospital in Bandung. Data from the American Academy of Ophthalmology also indicates the highest global prevalence of TED in middle-aged adults (Ramesh et al., 2023). TED generally occurs in adulthood due to changes in the immune system with aging, which can affect the development of autoimmune diseases like TED. Fluctuations in thyroid hormone levels as people age, a stronger genetic predisposition in adulthood, and prolonged exposure to environmental factors such as smoking in adulthood can trigger the onset of TED (Bahn, 2010; Stan and Bahn, 2010; Khalilzadeh, Noshad and Rashidi, 2011; Nugroho W., Limantoro and Arimadyo, 2019). The second most common age group was 51-60 years, followed by 21-30 years. The high prevalence in the 51-60 age group has been explained previously, as this group still falls within the category of middle-aged adults. Meanwhile, the high prevalence in the 21-30 age group in this study can be attributed to changes in smoking behavior, which has become more common in this young adult population. Smoking is one of the most major risk factors for the development of TAO as well as the progression of the disease (Bartalena and Piantanida, 2016).

Based on Table 1, it was found that all clinical features variables (according to the American Academy of Ophthalmopathy (AAO) criteria) were distributed among TED patients. The most prevalent clinical feature found was proptosis (94%). Similar to the findings in this study, Boesoirie et al. (2012) and Subramaniam et al (2023) reported 96% and 81% of their patients also had proptosis symptoms. According to the findings of a meta-analysis conducted by Chin et al. (2020), proptosis and eyelid retraction are the clinical manifestations of TED that are most often seen in the general population.

This study indicated a lower prevalence of eyelid retraction (22.73%) than some other studies that reported that this was the most frequent clinical sign found in TED patients. These other studies said that eyelid retraction was the most common clinical symptom (Ackuaku-Dogbe et al., 2017; Şahlı and Gündüz, 2017a). A lower prevalence of eyelid retraction was also reported by several studies in Asia, including by Boesorie et al. in Bandung (2012) (50%), Lim N et al in Singapore (2015) (62,1%), and Lim S et al in Malaysia (2008b) (53,4%). This difference in prevalence may be due to the fact that the margin reflex distance in Asian patients is shorter compared with Caucasian patients. Consequently, in Asian TED patients, eyelid retraction may not result in clear scleral exposure, complicating clinical findings on examination (Murchison, Sires and Jian-Amadi, 2009). One of the reasons why the rate of eyelid retraction was recorded as low in this study may be related to underreporting when recording medical records. This underreporting can occur when examiners tend not to note symptoms of eyelid retraction in patients who have been diagnosed with proptosis due to TED.

Chemosis and/or caruncular edema as well as erythema and/or eyelid edema in this study were found to be 12.5% and 60.23%. These findings were not much different from previous studies which reported that the incidence of these clinical features varied with range between 17.92% - 63.25% (Ackuaku-Dogbe, Akpalu and Abaidoo, 2017; Muralidhar, Das and Tiple, 2020). These two clinical features are non-specific features of TED and are manifestations of a soft tissue inflammatory process which is often an early sign of TED (Şahlı and Gündüz, 2017).

Only ten people participated in this study, which means that 11.36 percent of people had confined strabismus. The findings of this investigation supported the study by Hiromatsu et al. (2014) and Reddy et al. (2014) in recently diagnosed cases, 5–8% of those with strabismus were found to have the condition. Previous studies have also reported the prevalence of extraocular movement (EOM) restriction in 39%-47% of samples of TED patients (Lim et al., 2015; Muralidhar, Das and Tiple, 2020). In contrast, a recent study by Subramaniam et al. (2023) in a tertiary eye hospital in India reported that 38 out of 136 patients (28%) experienced EOM restriction. This difference can be understood because extraocular movement restriction or restrictive strabismus initially occurs due to inflammation causing swelling, and then it develops into secondary fibrosis. EOM becomes a characteristic of the disease that appears relatively later, so it may not be detected when considering newly diagnosed cases (Subramaniam, Yadalla and Rajagopalan, 2023).

In a recent study by Subramaniam et al. (2023) 4% of patients were found to have dysthyroid optic neuropathy (DON). Another study conducted by Muralidhar in India reported that 4 patients (3.77%) experienced DON (Muralidhar, Das and Tiple, 2020). These findings are not significantly different from an earlier study by Lim N.C.S et al. (2015), in which DON was observed in 4.6% of the subjects. These data align with the results of this study, where out of 88 TED subjects, only 3 patients (3.41%) had DON, making it the least commonly observed clinical manifestation in patients. DON is relatively rare because it is one of the emergency phenomena indicating that the TED cases are severe and have undergone extensive orbital fibrosis, accompanied by enlargement of extraocular muscles with tendon sparing, resulting in pressure on the optic nerve (Ben Simon et al., 2004; Thyparampil and Yen, 2016).

In this data, it can be observed that there were slightly more cases of bilateral TED than unilateral, with 48 patients (54.55%) compared to 40 patients (45.45%). Eshraghi et al. (2023a) stated that bilateral clinical manifestations are more commonly found in TED eye disease than unilateral manifestations. Additionally, unilateral cases can evolve into a bilateral form over time. However, according to Strianese (2013), asymmetric TED with initial unilateral proptosis is a relatively common occurrence compared to symmetric TED, in contrast to the findings in this study, which showed a slightly higher prevalence of patients with bilateral proptosis symptoms. In this study, the higher incidence of bilateral manifestations can be explained by the fact that the research was conducted at Dr. Soetomo Hospital, a tertiary referral center where most cases involve severe patient referrals, which can lead to initial patient visits with TED affecting both eyes.

Although TED is predominantly reported with hyperthyroidism, the disease can also occur in hypothyroidism or euthyroidism (McAlinden, 2014). In this study, it was found that 70.45% of the patients had hyperthyroidism, followed by 25% of patients with euthyroidism, and only 4.55% of patients had hypothyroidism. These results are supported by similar research that shows the same prevalence order. For instance, a study conducted by Patricia et al. (2015) at Cipto Mangunkusumo Hospital in Jakarta found a prevalence of 58.8% hyperthyroidism, 1.5% hypothyroidism, and

14.7% euthyroidism. It is plausible to believe that the higher incidence of TED in people with hyperthyroidism is attributable to the illness itself due to the correlation between the two, mainly because hyperthyroidism is identified as the most common TED-related thyroid disorder, particularly the one that caused by Grave's disease (Chin et al., 2020; Muñoz-Ortiz et al., 2020). Hypothyroid status in TED patients can occur due to natural changes in the disease, such as the transition from hyperthyroidism to hypothyroidism (referred to as "the thyroid gland burnout"), or the effects of excessive treatment for hyperthyroidism (Subramaniam, Yadalla and Rajagopalan, 2023). This was evident in the four patients in this study who had a history of hyperthyroidism and were undergoing hypothyroid treatment. As in this study, hyperthyroidism was diagnosed in four patients, all of whom had a history of hyperthyroidism and were undergoing treatment, resulting in a hypothyroid phase. The percentage of euthyroid patients in this study was consistent with the study by Restiadi (25%) and the study in India by Khurana et al. (36,67%), where some euthyroid patients had a history of thyroid dysfunction. This variation can be explained by the fact that ophthalmopathy symptoms can manifest before thyroid dysfunction (Mitchell and Pearce, 2013).

The tabulation results indicated a significant relationship between TED laterality and thyroid status, consistent with the study by Eshraghi et al. (2023a) which also observed a significant difference in the distribution of hyperthyroidism, hypothyroidism, and euthyroidism between the unilateral and bilateral groups. Other studies have also reported the association between thyroid status and TED laterality (Eckstein et al., 2009; Jang et al., 2012; Ponto et al., 2015).

The analysis of the differences between TED laterality and thyroid status (Table 3) showed results that were not entirely in line with previous studies, which stated an association between hyperthyroidism in developing bilateral TED and hypothyroidism in developing unilateral TED (Eshraghi et al., 2023). This study showed that compared to euthyroidism, hypothyroidism and hypothyroidism was associated with a higher incidence of bilateral TED (OR=4.222, p=0.006; OR=3.667, p=0.014). These differing results may be due to variations in the operational definition of thyroid status, where patients presenting for the first time at Dr. Soetomo General Academic Hospital often had subclinical hypothyroidism due to a history of hyperthyroidism, unlike other studies that only included patients with overt or primary hypothyroidism. Differences in the study samples became a significant influencing factor in the results.

This study revealed new information, indicating that hyperthyroidism and hypothyroidism were more associated with bilateral TED cases than unilateral ones, while euthyroid conditions tended to be more related to asymmetric or unilateral TED cases. Therefore, the laterality of clinical symptoms can be used to predict the thyroid status in TED patients.

Our research was not without limitations. Firstly, there was a risk of selection bias due to the retrospective design of the study, which meant that some medical records were incomplete or questionable at the outset. Secondly, some patients were followed up in different healthcare facilities with different laboratory analysis methods. Lastly, clinical examinations and recording of symptoms in patients' records were not standardised. Despite these limitations, our study, conducted in a tertiary referral hospital, could provide some reference for the clinical profile and thyroid status of TED patients, especially in the Asian population, where current data on this topic are limited.

CONCLUSION

This study concludes that there is correlation between TED laterality and thyroid status among patient TED. Follow-up studies are needed to investigate the susceptibility of abnormal thyroid status to developing bilateral TED.

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CONFLICT OF INTEREST

The authors declared there is no conflict of interest.

ETHICS CONSIDERATION

Ethical approval for this study was granted by the Ethical Committee for Health Research at Dr. Soetomo General Academic Hospital, Surabaya, under the reference number 1071/LOE/301.4.2/X/2022, issued on October 6, 2022.

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AUTHOR CONTRIBUTION

Each of the authors has played a role in every stage of this research, which included designing the study, collecting and analyzing data, manuscript drafting, and approval for the publication.

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