Thyrotropin Receptor Antibody as a Risk Factor for the Occurrence and Severity of Graves' Ophthalmopathy

Mohammad Robikhul Ikhsan[1], Nyoman Kertia[1], Supanji[2], Bambang Udji Djoko Rianto[3]

[1]Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[2]Department of Ophthalmology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[3]Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

ABSTRACT

Background. Graves' disease (GD) is an autoimmune disorder known to be the most common cause of hyperthyroidism. Thyrotropin receptor antibody (TRAb) might be involved in the occurrence and the disease process of Graves' ophthalmopathy (GO).
Objectives. This study aimed to evaluate whether TRAb levels are associated with the occurrence and severity of GO based on the clinical severity of The European Group on Graves' Orbitopathy (EUGOGO).
Methods. A case-control study of 44 patients with newly diagnosed Graves' disease (22 with GO compared to 22 without GO). Diagnosis of GO was made according to Bartley and Gorman's criteria. Level of thyrotropin receptor antibody was tested with electrochemiluminescence immunoassay (ECLIA) method. Assessment of the clinical severity of GO was documented with EUGOGO scores.
Results. Baseline characteristics were similar between 22 patients with GO compared to 22 patients non-GO group. Thyrotropin receptor antibody (TRAb) significantly increased in the GO group (11.223±7.116 IU/L) when compared to non-GO (6.720±3.442 IU/L; P=0.035). Multiple logistic regression analysis shows that 1 IU/L increase of TRAb has a 1.610-fold higher risk for developing GO. In the GO group, there is correlation between TRAb and the severity of GO-based on EUGOGO (r =0.794, P<0.001).
Conclusion. Thyrotropin receptors antibody is a risk factor for the occurrence and severity of GO-based on EUGOGO.

Keywords. Thyrotropin receptor antibody (TRAb), Graves' Ophthalmopathy, The European Group on Graves' Orbitopathy (EUGOGO)

ABSTRAK

Latar belakang. *Penyakit Graves (PG) adalah kelainan autoimun yang dikenal sebagai penyebab paling umum dari hipertiroidisme. Antibodi reseptor tirotropin (TRAb) mungkin terlibat dalam terjadinya dan perjalanan penyakit oftalmopati Graves (OG).*
Tujuan. *Penelitian ini bertujuan untuk mengevaluasi apakah kadar TRAb berhubungan dengan kejadian dan tingkat keparahan OG berdasarkan tingkat keparahan klinis dari* The European Group on Graves' Orbitopathy *(EUGOGO).*
Metode. *Studi kasus-kontrol terhadap 44 pasien dengan penyakit Graves yang baru didiagnosis (22 dengan OG dibandingkan dengan 22 tanpa OG). Diagnosis OG dibuat menurut kriteria Bartley dan Gorman. Kadar antibodi reseptor tirotropin diuji dengan metode* electrochemiluminescence immunoassay *(ECLIA). Penilaian tingkat keparahan klinis OG didokumentasikan dengan skor EUGOGO.*
Hasil. *Karakteristik awal serupa antara 22 pasien dengan OG dibandingkan dengan 22 pasien kelompok non-GO. Antibodi reseptor tirotropin (TRAb) secara signifikan meningkat pada kelompok O6 (11,223±7,116 IU/L) bila dibandingkan dengan non-OG (6,720±3,442 IU/L; P = 0,035). Analisis regresi logistik ganda menunjukkan bahwa peningkatan 1 IU/L TRAb memiliki risiko 1,610 kali lipat lebih tinggi untuk menjadi OG. Pada kelompok OG, terdapat korelasi antara TRAb dan tingkat keparahan OG berdasarkan EUGOGO (r =0.794, P<0.001).*

Kesimpulan. *Antibodi reseptor tirotropin merupakan faktor risiko terjadinya dan keparahan OG berdasarkan EUGOGO.*

Kata Kunci. Antibodi reseptor tirotropin (TRAb), oftalmopati Graves, *The European Group on Graves' Orbitopathy* (EUGOGO)

INTRODUCTION

Graves' disease (GD) is an autoimmune thyroid disease in which genetic and environmental factors interaction take place.[1] This disorder is known to be the most common cause of hyperthyroidism. The annual incidence ranges from 20 to 50 cases per 100,000 people. Incidence increases between the ages of 30 and 50, but can come up at any age.[2]

Thyrotropin receptor antibody (TRAb) is an antibody specifically used as a biomarker for GD diagnosis.[3] The level of this antibody increases in GD and mimics the effect of thyrotropin (TSH) resulting in hyperthyroidism.[4] The sensitivity and specificity of TRAb in diagnosing GD are 97% and 98%.[5] TRAb examination is important to differentiate GD from other causes of hyperthyroidism. This examination also has therapeutic and prognostic implications for GD.[6]

Graves' orbitopathy, also known as Graves' ophthalmopathy (GO), is a common extra-thyroid manifestation in GD and the most frequent orbital disorder in GD. In addition, GO is the leading cause of unilateral and bilateral proptosis in adults.[3,7] GO occurs in approximately 25% of GD patients. The estimated incidence of GO in the general population is 16 in women and 3 in men per 100,000 people per year, with severity occurring in 3-5% of cases.[8]

GO is due to autoimmune pathogenesis with important genetic and environmental influences, particularly smoking.[9] It presumably involves an antibody reaction against the thyroid-stimulating hormone receptor (TSHR) that results in the activation of T cells against tissues in the retro-orbital space that share similar antigenic epitopes with thyroid follicular cells.[10,11] The autoimmune complex intertwined with the inflammatory process, subsequent tissue remodeling, and fibrosis of the eye. Graves' ophthalmopathy progression give rise to various form of severity such as proptosis, strabismus, corneal ulceration. Furthermore, optic nerve entrapment may occur, consequently leading to blindness.[12]

The severity of Graves' ophthalmopathy assessment can be performed based on clinical symptoms and signs. The European Group on Graves Orbitopathy (EUGOGO) recommends that each patient with GO should be assessed for the clinical grade and severity.[13,14]

The relationship between TRAb levels and GO is still vague. Several studies have shown an association between GO and TRAb levels and how it is beneficial for detecting the tendency of GD to become GO.[15,16] Higher TRAb levels were found in GD patients with GO than those without GO.[9,17] TRAb levels correlated with the clinical severity of GO and were noticeable in moderate-to-severe GO with GD untreated.[18]

These immune processes generate an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and cytokine release that stimulate orbital

fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. Consequently, the extraocular muscles thicken, the adipose and connective tissues of the retroorbital increase in volume.[19] Thyrotropin receptor antibody (TRAb) may be useful in predicting the course of GD and the response to therapy. However, it is still unclear whether it can predict GO development.[14]

The presentation of GO also varies in different ethnic groups. GO may precede or follow endocrinologic manifestations. They typically present within 18 months apart.[10] GO was found to occur before GD in 23% of patients, concurrent with GD in 39%, and after GD in 37%.[20] We, therefore, designed a study to determine the risk factors of orbitopathy occurrence in patients with GD.

METHODS

A case-control study was performed to evaluate whether TRAb level is associated with the occurrence and severity of GO based on EUGOGO. The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki. The study was approved by the institutional ethical committee (Faculty of Medicine, Public Health and Nursing UGM).

The research was conducted at the Endocrine Clinic of Internal Medicine and the Eye Clinic of Dr. Sardjito Hospital, Yogyakarta from August 2021 to January 2022. All patients were previously diagnosed with GD (TRAb levels >1.75 IU/L) with symptoms of GO derived from clinical criteria according to Bartley and Gorman. The severity of GO was measured based on EUGOGO. Information regarding the demographic characteristics of all participants was acquired using well-structured questionnaires. A detailed history, physical examination, and laboratory test were carried out. Informed consent was obtained from all participants.

Inclusion criteria for this study are patients aged >18 years with newly diagnosed Graves' disease. The diagnosis of GD was made based on the clinical features of thyrotoxicosis, elevated thyroid hormones, suppressed thyrotropin (thyroid-stimulating hormone), and evidence of diffuse thyroid enlargement based on ultrasound imaging. The diagnosis of GO was established based on the criteria of Bartley and Gorman. Exclusion criteria included orbitopathy other than GD and a history of corticosteroid treatment for GO.

Detailed study design

In each eligible subject, the initial diagnosis for GO was performed by an endocrinologist. The patients were referred to the department of ophthalmology to undergo a clinical eye examination for the diagnosis of GO-based on the criteria of Bartley and Gorman and including the assessment of visual acuity, pupil response and color vision, extraocular movement and strabismus, lid measurements including palpebral aperture, marginal reflex distance, lid retraction, and Hertel's exophthalmometry.[10] The findings were classified into mild, moderate to severe, and sight-threatening (very severe) based on the EUGOGO classification.[21,22]

Statistical analysis

Frequency distribution was analysed in terms of means ± standard deviation for continuous variables and percentages for categorical variables. The Student's t-test or Mann–Whitney U-test was used for the comparison of continuous variables. The Chi-square test was used to compare categorical variables. Multivariate logistic regression analysis was performed to analyse the severity of GO (dependent variable) with various risk factors including duration of GD (months), gender, the level of free T4, and TRAb. *P* <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences version 21.0.

RESULTS

A total of 44 patients who met the inclusion criteria were included in the study. All patients were of Javanese ethnicity. Table 1 shows the baseline characteristics of subjects divided on the basis of patients with GO and without GO. Demographic, clinical, biochemical, and laboratory parameters were compared between the two groups. Baseline characteristics were similar between 22 patients with GO compared to 22 patients non GO groups (age: 30.91±6.06 vs. 30.68±6.63 years; gender: female 77.3% vs. 81.8%; duration from diagnosis 5.13±2.21 vs. 4.82±1.89 months). Thyrotropin receptor antibody (TRAb) significantly increased in the GO group (11.223±7.116 IU/L) when compared non GO (6.720±3.442 IU/L), P=0.035.

Table 2 shows multiple logistic regression to investigate the risk factor for the occurrence of GO in addition to TRAb and FT4. This regression analysis revealed that TRAb levels represent a significant risk factor for the occurrence of GO. Every 1 IU/liter increase of TRAb rises the risk for the occurrence of GO of 1.610-fold higher.

Thyrotropin Receptor Antibody (TRAb) levels were significantly correlated with clinical severity of G) based on the EUGOGO (r = 0.794, P<0.001) (Figure 1).

Table 1. Baseline characteristics are divided based on the existence of GO

Characteristic		Graves Ophthalmopathy Status				*P*
		Yes		No		
		n	%	n	%	
Age (years)		30.91±6.06		30.68±6.63		0.906
Gender	Female	17	77.3%	18	81.8%	1.000[$]
	Male	5	22.7%	4	18.2%	
Smoking	Yes	3	13.6%	3	13.6%	1.000[$]
	No	19	86.4%	19	86.4%	
Diabetes Mellitus	Yes	2	9.1%	2	9.1%	1.000[$]
	No	20	90.9%	20	90.9%	
Hypertension	Yes	3	13.6%	1	4.5%	0.607[$]
	No	19	86.4%	21	95.5%	

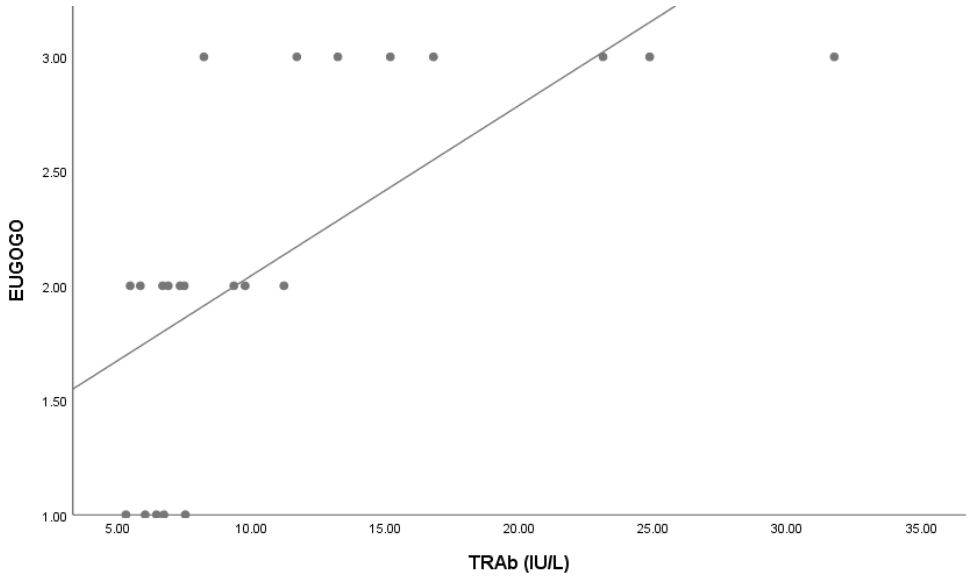
Family History	Yes	4	18.2%	3	13.6%	1.000$
	No	18	81.8%	19	86.4%	
Dermopathy	Yes	2	9.1%	2	9.1%	1.000$
	No	20	90.9%	20	90.9%	
Duration of diagnosis	(months)	5.13±2.21		4.82±1.89		0.611
TRAb (IU/L)		11.223±7.116		6.720±3.442		0.035*
FT4 (ng/dL)		3.33±0,84		2.99 ±1.24		0.305
EUGOGO		2 (1-3)		0		<0.001 *

*) Significant *P*<0.05, Mean ± SD): Independent T test, Mann Whitney, $) Fisher exact test

Table 2. Multiple logistic regression analysis of factors affecting the occurrence of GO

			95% C.I.for EXP(B)	
	P	OR	Lower	Upper
TRAb (IU/L)	.019*	1.610	1.080	2.399
Age (Years)	.280	.915	.779	1.075
Gender	.192	.125	.006	2.831
Smoking	.271	.171	.007	3.958
FT4 (ng/dL)	.708	1.162	.530	2.547
Diabetes Mellitus	.933	1.147	.048	27.429
Hypertension	.376	4.677	.154	142.046
Family History	.131	.090	.004	2.042
Dermatopathy	.226	.088	.002	4.512
Constant	.828	2.041		

Figure 1. Spearman correlation between TRAb and EUGOGO



DISCUSSIONS

Most patients with GD have improvement with conservative long-term

treatment. However, some patients develop progressive severe ophthalmopathy and require prolonged steroid treatment, irradiation, or surgical rehabilitation. Early decisions would be better if the course of GO could be predicted. Several risk factors including old age, gender, smoking, radioactive iodine treatment, higher level of TRAb, and abnormal thyroid function have been identified in several reports as possible risk factors for the occurrence of GO.

In this study, there was a statistically significant difference of TRAb level for the occurrence of ophthalmopathy ($P < 0.001$). Comorbidities such as hypertension and diabetes and others such as dermopathy were comparable between the two groups. This regression analysis in this study revealed that TRAb levels represent a significant risk factor for the occurrence of GO. A progressively increasing prevalence of GO was observed with increasing TRAb titers, and TRAb levels were an independent risk factor for GO.[23] The expression of thyrotropin receptors is higher in fibroblast compared with patients without ophthalmopathy, and the expression of thyrotropin receptors has a positive correlation with mRNA levels in orbital adipose tissue specimens of individual with GO.[24] Autoantibodies to thyroidal antigens, particularly TRAb, might be involved in the disease process of GO, and their detection may be of clinical benefit. A number of experimental and clinical studies support the theory of TRAb involvement in GO.[23]

In this study, TRAb levels were significantly correlated with the clinical severity of GO. Nabi and Rafiq conclude their study that TRAb levels were significantly correlated with the clinical severity of GO.[18] TRAb may represent an important switch that regulate the quality and amplitude of the immune response. It may also represent an important leading active phase of inflammation. Lymphocytes infiltrate the orbital tissue, release cytokines, allow orbital fibroblasts to proliferate, and produce mucopolysaccharides (glycosaminoglycans) that absorb water. As a result, the extraocular muscles thicken, and the volume of adipose tissue and connective tissue in the posterior orbit increases.

CONCLUSION

The current study suggests that TRAb is a risk factor for the occurrence of GO and correlates with the severity of GO-based on EUGOGO. Further research is needed by controlling confounding variables more strictly with a larger sample size. The results of this study can be considered as a guide to the diagnosis and therapy of Graves' patients with ophthalmopathy.

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