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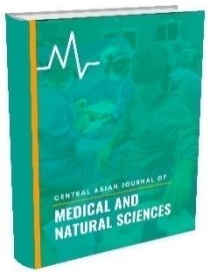

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The Frequency of Thyroid Stimulating Blocking Antibodies (TSBAbs) In Individuals with Newly Diagnosed AITD

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Abstract:

Introduction: Thyroid diseases as autoimmune (ATD) are autoimmune disorders presence of specific proteins autoantibody to of thyroid in the patient,sera i.e.,thyrotropin receptors (TSHr), Thyroid peroxidase (TPO), thyroglobulin (TG), Tgand antibodies ofTPO are utilized as clinical ATD markers, whereas antibodies of TSHr can either stimulating thyroid adenylatecyclase, resulting hyperthyroidism (TSAb), or blocking thyroid function, resulting in hypothyroidism (TSAb).

Methodology: This study was conducted on 30 patients Al- Haboby hospital and Al-Hussein hospital in Nasiriya city, Iraq (the period between February to September 2021. We studied 15 patients with Graves' disease GD [12 females and 3males]. measured using fully-automated by coobas e411analyzer (Roche Diagnostics).

Results: The most common GD presentations were diffuse goiter (100%), fine tremors (93.3%), symptoms of neuropsychiatric i.e.,hyperactivity, nervousness, and school performance beingpoor are communalcharacters in such children (80%), weight loss despite an increase inappetite (53.3%), ophthalmology (46.7%), and heat intolerance, sweating, palpitations (26.7 %).

Conclusion: No statistical significance associations were there between antibodies of thyroid and exophthalmos.There were no significant correlations between antibodies of thyroid and thyroid functions in GD.

Key words: AITDs GD, Hashimoto thyroiditis, TSHr abs, TPO abs, TG abs.

INTRODUCTION

Thyroid diseases are divided into two types based on the presence of anti antibodies of thyroid: AITD and non-AITD (NAITD). Thyroid autoimmunity is associated with two major clinical diseases:

hyperthyroidism (GD)and hypothyroidism (Hashimoto's thyroiditis) [1]. AITDs are autoimmune organ-specific disorders categorized by the existence of autoantibody to thyroid specific proteins in the patient's sera i.e.,Thyroid peroxidase (TPO),thyroglobulin (TG), and thyrotropin receptors (TSHr) are two enzymes involved in thyroid peroxidase [2].Antibodies as TPO and Tg are utilized as clinical ATD markers, whereas antibodies ofTSHr can either thyroid adenylatecyclasestimulating, resulting in hyperthyroidism (TSAb), or blockingfunction of thyroid, resulting in hypothyroidism (TSAb) [3].Other types of TSH-R Abs might be existing, including anantibody as receptor whichperformances as anantagonist of TSH, known as TSH-R Abs (TSB-Ab) Blocking, and a neutral antibodies form of no receptor worthless effect. TSHR Abs Blocking might be associated with the stimulatory kind and might as well predominate in some patients following treatment of radioiodine, surgery or anti-thyroid medications are options. TSHR Abs Blocking are as well detected in patients of 15% with thyroiditis asautoimmune, principally in those who do not have a goiter (The atrophic variety). The use of currently available methods does not allow for the detection of TSHR Ab in the general population[4]. Autoantibodies of Tpoand Tgare secondary reactions to injury of thyroid and of nodisease causing. Both antibodies types are polyclonal, and while they belong to the class of IgG, they are not limited to a IgGsingle subclass. Tpo Abs and Tg Abs levels both associate with lymphocytic thyroid gland infiltration, but they are not passing disease to fetusfrom mother. As a result, antibodies of thyroid to Tpo and Tg do not cause disease. Tpo Abs, in particular, are relatedto thyroid damage and lymphocytic infiltration [5].

Clinical importance of Tg Abs and TPO Abs:

In the population as general, autoantibodies to TPO and Tg are mutual and are nearly 5 times more mutual in females than in males at all ages [6]. Positive Tg Abs and TPOAbs levels are associated with mainAITD[7]. Measurements of antibody might as well be beneficial in sub-clinically prognosticallyhypothyroid patients (those with TSH being elevated but normal levels of T4), because the overt hypothyroidism rate in patients with a slightlyamplified TSH level and +ve thyroid auto-antibodies is about 3% to 5% per year [8].Antibodies to Tpo and Tg are as wellnoticeable in 50% to 90% of GD patients, indicating the connected thyroiditis which is histologically visible. Even though such autoantibodies presence favoritisms the autoimmune cause diagnosis of hyperthyroidism in excess of further causes, it does not rule out other possibilities, In this context, the exams are neither specific nor sensitive, and can just be interpreted as part of a clinical scenario. Limited evidence suggests that higher Tg Abs and Tpo Abs titers in GDof hyperthyroid patients are future predictive hypothyroidism following anti-thyroid drug treatment [9].

Thyroid-Stimulating Hormone Receptor (TSH-R):

TSH interacts with the extracellular amino-terminal domain of its receptor to activate the G-protein that is associated with it. GTP replaces bound GDP, and the G protein subunit dissociates. A Gs-protein subunit activates adenylatecyclase, whereas a Gq-protein subunit phosphorylates and activates phospholipase C. The adenylatecyclase enzyme promotes the conversion of ATP to cAMP that then phosphorylates and stimulates protein kinase A (PKA). Phospholipase C promotes the phosphatidyl inositol 4,5-bisphosphate (PIP2) conversion to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3).Such, consecutively, produce Ca2+ from intracellular stores and stimulate protein kinase C. TSH concentrations much higher in humans are required to activate the inositol pathway. TSH-R belongs to the G protein-coupled receptor family. TSH or a subset of TSH-R antibodies with stimulatory activity activate TSH-R, resulting in intracellular signaling via the cyclic adenosine monophosphate (cAMP) pathway [10]. The human TSHR (hTSHR) is the prime GDauto-antigen, as evidenced throughmice hyperthyroidism following immunization with hTSHR antigen [1]. TSH-R Abs in patients of GD are denoted to as agonist or stimulatory TSHR Abs- (TSAB). Other types of TSH-R Abs may be existing, including an antibody ofreceptor whichbehaves as an antagonistfor TSH, known as Blocking TSH-R

Abs (TSB-Ab), and a neutral antibodies form with no functional receptor effect. Blocking TSHR Abs might occur concurrently with the stimulatory kind and might as well predominate in definite patients following radioiodine treatment, drugs as anti-thyroid, or thyroid hormone replacement therapy, or even surgery Blocking TSHR Abs are also detected in patients of 15% with auto-immune thyroiditis, principally in those who do not have a goiter (The atrophic variety). The use of currently available methods does not allow for the detection of TSHR Ab in the general population [11].

GD is a syndrome that is distinguished by diffuse goiter and hyperthyroidism [12].

Epidemiology: is uncommon in children and adolescents, occurring at a rate of 0.1—3.0 per 100,000. GD is further mutual in females than males (7 to 10:1) and becomes additional common following puberty [13].

Etiology: Most researchers agree that GD is a disease being multi-factorial produced by a complex genetic interplay, environmental and hormonal influences whichresult intolerance loss to antigens of thyroid and the sustained immune response initiation directed at thyroid and unidentified orbital antigens [12].

Role of TSHR antibodies:

TSH receptor binds to TSHRAbs, stimulatingadenylatecyclase, inducinggrowth of thyroid, elevate vascularity, and lead to an increase in production of hormone ofthyroid and GDsecretion. TSHRAbs in GD patients are denoted as agonist or stimulating TSHRAbs. The point that TSHRAbs are just found in AITDs patients suggests that the antibodies are disease-specific, as opposed to the antibodies prevalence of TPO and TG in the general population. patients with GDthat untreated hyperthyroid have noticeableTSHRAbs with activity of thyroid-stimulating in 80-100 percent of cases. TSHRAb levels are reduced by disease treatment and, if they persist, are predictive of failure to respond to antithyroid drug treatment. After GD treatment, TSHR-blocking autoantibodies may become the dominant type [14].

MATERIALS AND METHODS

2.1. Circulating auto-antibodies:

TG and TPO Antibodiesare found in 50-90 percent of GD patients. Despite the existence of these auto-antibodies that favoring an auto-immune hyperthyroidismcause over another causes, the exams are neither specific norsensitive in such setting and can just be interpreted being part of scenarioas clinical. Limited evidence suggests that higher TG Abs and TPO Abs titers in hyperthyroid GDpatients that are of future predictive hypothyroidism following anti-thyroid drug treatment [13]. The assayof TRAb is a highly sensitiveandspecific test for hyperthyroid GD. More than untreated patients of 90% test +ve. It is required in specific cases where the nature of the thyrotoxicosis must be confirmed or if the thyroid function orclinical picture exams are not obvious. Suchcases includingpregnancythyrotoxicosis, GDnodular variants which ought to be distinguished from goitertoxic nodular, and exophthalmospatients without thyrotoxicosis (euthyroid GD) [14].

2.2. Subjects and methods:

This study was conducted on 30 patients Al- Haboby hospital and Al-Hussein hospital in Nasiriya city, Iraq (the period between February to September 2021. We studied 15 patients with GD [12 females and 3males] [80% : 20%] age range = 6-18 years, mean age± SD 13.2 ±3.5 years .

2.3. Sampling:

5 ml whole blood obtained by vein puncture, allowed to clot and sera were separated for analysis of thyroid profile promptly and aliquots stored at -70 till analysis time for antibodies.

2.4. Laboratory methods:

Serum free thyroid hormones, Serum TSH, antibodiesof Anti-thyroglobulin [TG AB] , antithyroperoxidase [TPO AB] antibodiesand (TSHr Abs):measured using fully-automated by ElectroChemiLuminescence (ECL) immunoassay on the coobas e411analyzer (Roche Diagnostics) according to manufacturing protocol.

2.5. Statistical analysis:

Statistical analysis of the present study was conducted using the spss 22.

RESULTS

Clinical presentation of GD was as follow :100% presented by neck lump ,93.3%by fine tremors,80%by nervousness,53.3%by weight loss,46.7% by protruding eyes, while only 26.7%presented by palpitation. By clinical examination 100% of patients with GD had medium to large goiter ,46.7%had exophthalmos, and 20% had pulse more than 100/min.

Table 1. demographic & clinical presentation of GD.

	Frequency	%
Age(years) range	6- 18	
Age(years) mean ±sd	13.2 +3.5	
Female:male	12 :3(80%) (20%)	
Complaint		
neck lump	15	100 %
fine tremors	14	93 %
Nervousness	12	80%
weight loss	8	53 %
protruding eyes	7	46 %
Palpitation	4	26 %
Signs		
medium to large goiter	15	100 %
Exophthalmos	7	46 %
pulse more than 100/min	3	20 %

Table 2. Number of patients(Percentage) who has positive antibodies of thyroid.

Group No	n	patients with AITD &control	Gender thyroid disease &control (female:male)	TGAB	TPOAB	TSHRAB
1		Untreated Graves'disease	12-3	46.70%	93.30%	53.30%
2		Graves'disease after follow up	12-3	46.70%	100.00%	40.00%

Table 3. thyroid functions of all patients before &12 months after follow up.

Group	thyroid function	before 12 months mean±SD)	after 12 months of follow up (mean±SD)	significance
Graves'disease	FT3	5.9±0.4	4.3±0.9	0.001
	FT4	3.6±.0.6	1.9±0.3	0.001
	TSH	0.6±0.5	1.1±0.6	0.049

As regard thyroid functions:Free T4&T3 are significantly decrease after follow(12months) and there is border line significance (.05)increase of TSH after follow up

Table 4. antibodies of thyroid of all patients before &12 months after follow up.

Group	antibodies of thyroid	before 12 months mean±SD)	after 12 months of follow up (mean±SD)	significance
Graves'disease	TGAB	118.3±118.5	96.9±74.6	0147
	TPOAB	104.3±.143.2	110.5±93.9	0.317
	TSHRAB	27.8±56.7	19.3±29.7	0.005

TG Abs decrease following treatmentoftwelve months, but not significantly. TPO Abs increase following treatment of twelve months, but not significantly. TSHR Abs, on the other hand, significantly decrease after treatment.

Table 5. Correlations between antibodies of thyroid and both clinical data and thyroid functions in GD.

Spearman's rho			TG abs	TPO abs	TSHR abs
	Exophthalmos	Corr. Coif.	.155	.526	-.186
		Sign. (2-tailed)	.582	.044	.507
		N	**15**	**15**	**15**
	fT3	Corr. Coif.	.122	-.262	.081
		Sign. (two-tailed)	.665	.346	.775
		N	**15**	**15**	**15**
	fT4	Corr. Coif.	-.224	-.224	.275
		Sign. (two-tailed)	.423	.423	.321
		N	**15**	**15**	**15**
	TSH	Correlation Coefficient	-.103	-.162	.403
		Sign. (two-tailed)	.716	.564	.137
		N	**15**	**15**	**15**

**Corr. is significant statistically at the.01 level (two-tailed)

* Corr. is significantstatistically at the.05 level (two-tailed).

antibodies of thyroid and exophthalmos had no statistically significant correlations. antibodies of thyroid and thyroid functions were also found to have non-significant correlations (FT3, FT4 and TSH).

DISCUSSION

We examined the clinical and laboratory data of 15 children (their ages mean) at first presentation was of range 6-18 years being =13.23.5, with a ratio of females to males (4:1). with newly diagnosed GD whose diagnosis was based on both clinical and laboratory evidence (suppressed TSH, elevated free T3, T4 , increase uptake of I 123 and signs of Graves' ophthalmopathy when present). Patients who had eyelid retraction, lid lag or proptosis were defined as subjects with ophthalmopathy. The most common presentations were diffuse goiter (100%), fine tremors (93.3%), These children frequently exhibit symptomsas neuropsychiatric i.e.,hyperactivity, nervousness, and poor performanceas academic (80%), weight loss despite an increase in appetite(53.3%), ophthalmology (46.7%) and heat intolerance, sweating, palpitations (26.7%). The fifteen patients were under treatment by anti thyroid drugs (methimazole) and beta blocker agonist for 12 months, with significant decrease in both FT3 and FT4 (p=0.001) and increase in TSH (p=0.05)

Also; 30 serum samples obtained from another fifteen children with suspected Hashimoto thyroiditis; whose diagnosis was based on both clinical and laboratory evidence (elevated TSH, suppressed free T3,T4 and decrease uptake of I 123), treated by L-thyroxine (T4) for 12 months without significant changes in FT3, FT4 or TSH. Their mean age at first presentation was of range 5-18 years being =11.6±4.2 years, females to males ratio was (11:4). All were presented by goiter, 20% with decreased activities, 13.3% had constipation, and only 6.7% (one patient) had short stature. These clinical data are in agreement with other researchers [13]. Ophthalmopathyof Graves' (GO) is linkedclinically to AITD, and auto-antibodies to antigensas thyroidal, particularly the TSH-receptor (TRAb), may play a role in the processof disease. On the other hand, there is evidencegrowing in whichTRAb are linked to GO at the diseasestart [15]. While in our study; there were no correlations between antibodies of thyroid and exophthalmos or thyroid functions (FT3, FT4 and TSH) at the onset of GD.

CONCLUSIONS

There were no statistically significant associations between antibodies of thyroid and exophthalmos. There were no significant correlations between antibodies of thyroid and thyroid functions in GD.

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