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COMPARISON OF CARDIAC ARRHYTHMIA TYPES BETWEEN HYPERTHYROID PATIENTS WITH GRAVES' DISEASE AND TOXIC NODULAR GOITER

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Abstract

Purpose. Previous studies have demonstrated the relationship between hyperthyroidism and increased risk of cardiac arrhythmias. The most common causes of hyperthyroidism are Graves' disease (GD) and toxic nodular goiter (TNG). The aim of our study was to demonstrate if the underlying mechanism of hyperthyroidism, in other words autoimmunity, has an impact on the type of cardiac arrhythmias accompanying hyperthyroidism.

Method. Twenty patients with TNG and 16 patients with GD who had overt hyperthyroidism were included in the study. Age, sex, thyroid hormone levels, thyroid autoantibody positivity, thyroid ultrasonography and scintigraphy results were recorded. 24-hour Holter ECG monitoring was performed in all patients.

Results. Mean age was significantly higher in the TNG group compared to the GD group (62.9±11.5 *vs*. 48.9±8.6 years, p=0.001). Free T3 was significantly higher (7.87±3.90 *vs*. 5.21±1.53 pg/mL, p=0.033) in the GD group while free T4 and TSH levels were similar between the two groups. In 24-hour Holter ECG recordings nonsustained ventricular tachycardia (VT) rates were significantly higher in the GD group than in TNG group [18.75% (n=3/16) *vs*. 0% (n=0/20), respectively, (p=0.043)]. Paroxysmal atrial fibrillation (AF) rates were significantly higher in the TNG group compared to GD group [(30% (n=6/20) *vs*. 0% (n=0/16), respectively, (p=0.016)].

Conclusion. Although free T3 levels were lower, paroxysmal AF rates were found significantly higher in the TNG group which may be associated with significantly higher age of this group. On the other hand, higher rate of nonsustained VT in the GD group may be related to either significantly higher free T3 levels or autoimmunity.

Key words: Hyperthyroidism, arrhythmia, ECG monitoring, Graves' disease, toxic nodular goiter.

INTRODUCTION

Several complex actions of thyroid hormones on cardiac muscle and blood vessels lead to a series of cardiovascular changes and complications including increased cardiac output, cardiac contractility, systolic blood pressure, heart rate, pulmonary artery pressure and cardiac arrhythmias in hyperthyroidism (1, 2). The most common causes of hyperthyroidism are Graves' disease (GD) and toxic nodular goiter (TNG). In GD autoimmunity is the underlying mechanism of hyperthyroidism while TNG is characterized by autonomy and hyperfunctioning in one or more thyroid nodules.

Sinus tachycardia is the most common form of arrhythmia in hyperthyroid patients as thyroid hormone is a direct stimulator of sinus node pacemaker (1, 3). The prevalence rates of supraventricular arrhythmias especially atrial fibrillation (AF) vary greatly between 1%-15% (2). Atrial flutter and other supraventricular tachyarrhythmias (SVT) including paroxysmal atrial tachycardia have been reported less commonly and premature ventricular contractions (PVCs) and ventricular tachycardia (VT) are rare (2).

In euthyroid patients a possible role of autoimmunity in the development of cardiac arrhythmias has been suggested by a few pathophysiological mechanisms. Cardiac conduction defects, brady- and tachyarrhythmias have been reported in some autoimmune rheumatological diseases like systemic sclerosis, systemic lupus erythematosus, and polymyositis (4, 5). Antibodies causing deposition of immune complexes in cardiac tissue affecting the conduction system of the heart was one of the documented underlying mechanisms (4). Secondly, transplacental passage of anti-SSA/Ro and anti-SSA/La antibodies were suggested to cause fetal conduction disturbances (6). Additionally, an association between different autoantibodies such as anti-β1 adrenergic, anti-β2 adrenergic, anti-M2, anti-Na/K-ATPase or anti-myosin heavy chain receptor and development of once considered "idiopathic" cardiac arrhythmias

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has been demonstrated (7-10) and a coined new term called "autoimmune cardiac channelopathies" has been suggested in a recent article (11).

In support of these findings previous studies have demonstrated activating autoantibodies to the β-1 adrenergic, β-2 adrenergic and M2 muscarinic receptors in the serum of patients with GD and established an association between AF and β-1 adrenergic and M2 muscarinic receptor autoantibody positivity (12-14). In the view of these results, the present study aims if there are any differences between the type of cardiac arrhythmias seen in hyperthyroid patients with GD and TNG.

PATIENT AND METHODS

Drug-naive hyperthyroid patients with TNG and GD were recruited consecutively from the endocrinology outpatient clinic. Patients were also evaluated by cardiology clinic and patients with valvular disease, heart failure, arrhythmia, acute coronary syndrome, antiarrhythmic drug use or being under treatment with a medication that could affect heart rate and rhythm, having a pacemaker and bundle branch block, were excluded. To rule out co-existing thyroid autoimmunity, thyroid autoantibody positivity was also checked in TNG patients and five patients with anti-thyroglobulin (anti-Tg) and/or anti-thyroperoxidase (anti-TPO) positivity were excluded from the study. After exclusion, there were twenty patients with TNG and sixteen patients with GD in the study group. Age, sex, thyroid hormone levels, thyroid autoantibody positivity, transthoracic echocardiography, thyroid ultrasonography and scintigraphy results were recorded. 24-hour ambulatory Holter ECG recordings were evaluated in terms of maximum and minimum heart rates, and existence of supraventricular premature contractions (SVPCs), SVT, AF, PVCs and nonsustained VT. Paroxysmal AF is defined as lasting more than 30 seconds and terminating spontaneously. SVT is defined as three and more consecutive supraventricular complexes at a rate >100 bpm, such as reentry tachycardia or multifocal atrial tachycardia, but not including atrial fibrillation or flutter. Nonsustained VT is defined as three and more consecutive premature wide QRS complexes with a heart rate of > 100 bpm.

Venous blood samples were collected for free T3, free T4, TSH, anti-Tg and anti-TPO. Analyses of free T3, free T4, TSH, anti-Tg, and anti-TPO were performed on DxI 800 Access Immunoassay (Beckman Coulter Inc., Brea, CA, USA) using a direct chemiluminescence detection system. Tc99m thyroid scintigraphy was performed with gamma camera interfaced dedicated computer system (Siemens E.CAM, Siemens Medical Systems Inc., Hoffman Estates, IL, USA). Thyroid ultrasonography was performed with an ultrasonography device (LOGIQ P6; GE Healthcare, Milwaukee, USA) equipped with a 10 MHz linear probe. Standard echocardiography was performed using the Philips Envisor C HD echocardiography device (Philips Medical Systems, Andover, MA, USA) using a 2 to 4 MHz probe. 24-hour ambulatory Holter ECG recordings were performed using Lifecard CF Holter Recorders (Reynolds Medical, Hertford, UK) and data from the monitors were analyzed by software (Pathfinder Digital Holter Analyzer).

Data were analyzed by using SPSS for Windows version 15.0 (SPSS Inc. Chicago, IL, USA). Baseline characteristics were expressed in numbers and percentage. Continuous variables were expressed as mean ± standard deviation. Mann-Whitney U test was used to compare differences between the two groups. Chi-square test was used for categorical variables. Pearson correlation analysis was conducted for association between the continuous variables, p value <0.05 was considered to be statistically significant.

Informed consents were received from all patients. Ethics committee approval was given by the Necmettin Erbakan University Human Research Ethics Committee (PN Protocol 2012/134) on 04/05/2012.

RESULTS

The baseline characteristics and 24-hour Holter ECG monitoring results are summarized in Table 1. Mean age was significantly higher in the TNG group compared to GD group (62.9±11.5 *vs*. 48.9±8.6 years, p=0.001). There was no significant difference in terms of hypertension (12.5% *vs*. 25%, p=0.426), diabetes mellitus (0% *vs*. 0%) and BMI (26.9±4.25 *vs*. 27.88±6.59, p=0.607) between the GD and TNG groups. There was no significant difference in terms of office blood pressure measurements, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left atrium (LA) diameter, between the GD and TNG groups.

Free T3 levels were significantly higher in the GD group compared to TNG group (7.87 ± 3.90 pg/mL *vs*. 5.21 ± 1.53 pg/mL, p=0.033), while free T4 and TSH levels were similar between the two groups.

Table 1. The baseline characteristics, echocardiography and 24-hour Holter ECG monitoring results in patients with Graves disease or nodular goiter

	Graves' disease group n=16	Toxic nodular goiter group n=20	P value
Age (mean±SD)	48.9±8.6	62.9±11.5	**P=0.001**
Male/Female	6/10	7/13	P=0.877
Hypertension (%)	12.5% (n=2/16)	25% (n=5/20)	P=0.426
BMI (kg/m^2)	26.9±4.25	27.88±6.59	P=0.607
LVEF (mean±SD)	59.56±3.07	58.90±3.05	P=0.524
LVEDD (mean±SD)	4.68±0.272	4.73±0.331	P=0.682
LVESD (mean±SD)	2.73±0.232	2.80±0.320	P=0.330
LA (mean±SD)	3.33±0.464	3.47±0.572	P=0.442
Systolic blood pressure (mean±SD)	127.19±12.31	136.90±19.98	P=0.158
Diastolic blood pressure (mean±SD)	76.25±8.06	80.60±12.80	P=0.352
Free T3 (mean±SD)	7.87±3.90	5.21±1.53	**P=0.033**
Free T4 (mean±SD)	2.12±1.00	1.65±0.68	P=0.220
TSH (mean±SD)	0.040±0.017	0.035±0.032	P=0.124
Maximum Heart Rate (mean±SD)	128.06±19.04	127.70±21.49	P=0.958
Minimum Heart Rate (mean±SD)	68.25±9.59	63.95±9.45	P=0.187
SVPCs [median (min-max)]	3.50 (0-1077)	17 (0-3568)	P=0.404
SVT (%)	12.5% (n=2/16)	25% (n=5/20)	P=0.309
Paroxysmal AF (%)	0% (n=0/16)	30% (n=6/20)	**P=0.016**
PVCs [median (min-max)]	8.50 (0-7210)	15 (0-661)	P=0.648
Nonsustained VT (%)	18% (n=3/16)	0% (n=0/20)	**P=0.043**

BMI: Body mass index, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LA: Left atrium, SVPCs: Supraventricular premature contractions, SVT: Supraventricular tachycardia, AF: Atrial fibrillation, PVCs: Premature ventricular contractions, VT: Ventricular tachycardia.

In 24-hour Holter ECG recordings: there was no significant difference in terms of maximum and minimum heart rates, SVT, SVPCs and PVCs between the two groups. Paroxysmal AF rates were significantly higher in the TNG group compared to the GD group (30% *vs*. 0%, p=0.016), while nonsustained VT rates were higher in the GD group compared to the TNG group (18.75% *vs*. 0%, p= 0.043). There were positive correlations between maximum heart rate and free T3 (r= 0.418, P=0.014) and free T4 (r=0.387, p=0.02). There were positive correlations between minimum heart rate and free T3 (r=0.484, p=0.004) and free T4 (r=0.575, p<0.01). There was no correlation between paroxysmal AF rates and thyroid hormone levels. There were positive correlations between nonsustained VT rates and free T3 (r=0.758, p<0.01) and free T4 (r=0.567, p<0.01).

DISCUSSION

The present study demonstrates that in overt hyperthyroidism patients with TNG have an increased incidence of paroxysmal AF compared to GD, while patients with GD have an increased incidence of nonsustained VT compared to TNG. These results should be interpreted keeping in mind that: TNG patients were significantly older (62.9±11.5 *vs*. 48.9±8.6ys, p=0.001) compared to GD patients, while free T3 levels were significantly higher (7.87±3.90 *vs*. 5.21±1.53 pg/mL, p=0.033) in GD patients compared to the TNG group.

There are several studies suggesting a possible difference between the cardiovascular complications of hyperthyroidism in patients with GD and TNG which may be originating from autoimmunity as a unique feature of GD and the frequently older age of presentation in TNG (3, 12-14). In 2013 Brandt *et al.* in a Danish population based register study, reported a total of 1291 patients with GD and 861 with TNG, treated in a hospital setting and followed for a mean period of eleven years (15). Both GD and TNG were associated with an increased all-cause mortality. But the causes of death differed between the two phenotypes with cardiovascular mortality being significantly higher in GD. Meanwhile, recent studies have demonstrated that autoantibodies against angiotensin II-1, β1-adrenergic, M2 muscarinic G protein-coupled receptors were significantly increased in the serum of patients with different types of cardiomyopathies and primary cardiac arrhythmias, suggesting autoimmunity contributing to the pathogenesis (9, 10, 16, 17). Likewise the pathogenesis of GD is attributed to autoantibodies that activate the G protein-coupled thyrotropin receptor (18). Stavrakis *et al.* have tested the effects of immunglobulin G (IgG) purified from GD patients with or without AF on isolated canine Purkinje fiber contractility (12). Contractility bioassays demonstrated

activating autoantibodies to the β-1 adrenergic and M2 muscarinic receptors in IgG samples and the rates were significantly higher in GD patients with AF compared to patients with sinus rhythm (12). In this study, age of GD patients with AF were significantly higher than in GD patients with sinus rhythm (12). In a further study by the same group evaluating autoantibody positivity in several forms of thyrotoxic patients and a control group, toxic multinodular goiter, subacute thyroiditis and control group patients had a low prevalence of autoantibodies. β-1 adrenergic, β-2 adrenergic and M2 muscarinic receptor autoantibody activities were elevated in GD. But only β-1 adrenergic and M2 muscarinic receptor autoantibodies appeared to be related to concurrent AF as their activities were significantly higher in GD patients with AF compared to those with sinus rhythm (14). In another study, angiotensin II-1 receptor antibody (AT1-AA) rates were measured in GD patients with and without cardiovascular complications (13). The age and rate of AT1-AA positivity in GD patients with cardiovascular complications were significantly higher than those of GD patients without cardiovascular complications. Also within patients with cardiovascular manifestations of GD, the ratios of left atrial and ventricular enlargement and the frequency of AF were significantly higher in the AT1-AA positive group compared to the AT1-AA negative group (13). In their detailed review on cardiovascular involvement in hyperthyroidism, Biondi and Kahaly have presented combined data from three studies including TNG, GD and control patients, each group including fifty patients (3). In 24-hour Holter monitoring both SVPCs and ventricular arrhythmias were significantly more prevalent in untreated TNG patients compared to GD patients and controls. This difference was partly attributed to significantly higher age of TNG patients compared to GD patients (3). The significance of age was also confirmed in a study including only GD patients in which 31% of patients ≥40 years old had AF compared to none <40 years old (19). Left atrial enlargement (diameter >40 mm) rates also increased significantly when patients were ≥40 years old and had AF, compared to having AF but being <40 years old or being only ≥40 years old (prevalence 94%, 7% and 2%, respectively). Similar to the abovementioned studies the mean age of TNG group was significantly higher than of GD group in our study although the mean age of GD patients was also > 40 years old (48.9±8.6 years) which may partially offset the effect of age difference between the two groups. The echocardiographic LVEF, LA and left ventricular diameters were also similar between the two groups. Furthermore, there was no statistically significant difference between cardiometabolic risk factors, such as: hypertension, DM, BMI and office blood pressure measurements between the two groups. Therefore, if we ignore the age difference, we can say that cardiometabolically similar groups were compared.

In 24-hour Holter ECG recordings, maximum and minimum heart rates were similar in two groups; notwithstanding, the maximum and minimum heart rates were positively correlated with free T3 and free T4, in the study population. There was no correlation between paroxysmal AF rates and thyroid hormone levels. Although not statistically significant, the incidence of SVPCs and SVT was higher in TNG group, when compared to GD. These findings may support the significantly higher AF incidence observed in TNG patients. SVPCs are of minor clinical significance, but they may be harbingers of SVT or AF. It is known that the incidence of AF in patients with paroxysmal SVT is higher than in an age-matched normal population, reaching as high as 12% during a mean 1-year follow-up (20).

Besides the formation of G protein-coupled receptor autoantibodies, autoimmunity may induce arrhythmia in GD due to structural changes in the heart. In an autopsy study including twenty-seven patients with GD, mild myocardial edema, nonspecific myocyte hypertrophy and interstitial fibrosis consistent with idiopathic dilated cardiomyopathy were observed (21). Increased prevalence of reversible dilated cardiomyopathy (22), myxoid valve degeneration possibly due to accumulating mucopolysaccharides (3) and pulmonary arterial hypertension which may be secondary to autoimmune-mediated pulmonary vascular remodeling (3, 23) have also been reported in patients with GD.

Another difference noted in the cardiovascular outcomes of TNG and GD patients may be development of coronary artery spasm (CAS). In two case series studies, patients with and without thyrotoxicosis who were diagnosed with CAS at a single institution were retrospectively assessed in terms of clinical characteristics (24, 25). Choi and colleagues reported three hundred and twenty-five patients with CAS of whom eight had thyrotoxicosis all due to GD (24). Lee and colleagues evaluated data of four hundred and thirty CAS patients with (n=32) and without (n=398) thyrotoxicosis (25). Normal coronary angiogram rates were similar between euthyroid and thyrotoxic CAS subjects. Among thyrotoxic patients 65% had GD

while TNG was the second most common etiology (18%). Within the thyrotoxic patients the mean free T4 level was the highest in patients with GD, and most of the left main vessel involvement of spasms, intractable spasms, myocardial infarctions, or adverse outcomes developed in patients with GD (25).

In contrast to the relatively high incidence of supraventricular arrhythmias, ventricular arrhythmias are uncommon in hyperthyroidism. In this regard, a significantly higher incidence of nonsustained VT in the GD group compared to the TNG group may be a new finding. There are anecdotal case reports of patients with VT and thyrotoxicosis (26, 27), ventricular fibrillation in GD patients with (28, 29) and without hypokalemic periodic paralysis (30, 31) in the literature. The presence of nonsustained VT may increase the risk for more malignant dysrhythmias such as sustained VT or ventricular fibrillation that can cause sudden cardiac death (32). Significantly higher rates of nonsustained VT in GD patients in our study may hence increase the risk for death in this group and can be one of the explanations for the higher cardiovascular mortality reported in patients with GD (15).

Like AF (12-14), autoimmunity may be playing a role in predisposing GD patients for development of ventricular arrhythmias. Autoantibodies have been implicated in the development of ventricular tachyarrhythmias in patients with connective tissue disease who were positive for anti-Ro/SSA antibodies (8, 17, 33). Previously, in patients with primary ventricular arrhythmias, idiopathic dilated cardiomyopathy and Chagas' disease a strong correlation between anti-β1 adrenergic autoantibodies and ventricular arrhythmias has been detected (34-37). Considering the positive correlations between nonsustained VT rates and thyroid hormone levels, in our study; another possible reason may be the significantly higher free T3 levels in the GD group compared to the TNG group, although it is not straightforward to interpret the impact of higher T3 levels in terms of triggering arrhythmia as the concentrations of T4 and T3 in cells vary according to the amounts of each hormone that are transported or diffuse into the cells, and the type of deiodinases in these cells.

The limitations of the present study are: the significant age difference between TNG and GD patients and the limited patient number. Two age-matched groups with larger patient numbers would definitely increase data strength and measurements of β-1 adrenergic and M2 muscarinic receptor autoantibodies could bring additional implications regarding the pathophysiology of arrhythmias. On the other hand, exclusion of thyroid autoantibody positive patients from the TNG group is a unique feature and detection of a significantly increased rate of nonsustained VT in the GD group is a new finding of our study. Further studies evaluating the correlation of β-1 and M2 receptor autoantibodies with cardiac arrhythmias in age-matched and larger sample size groups may better clarify the role of autoimmunity in the pathophysiology of arrhythmias seen in hyperthyroidism.

Conflict of interest

The authors declare that they have no conflict of interest.

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