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Evaluation of Autoimmune Thyroid Disease in Patients with Mitral Valve Prolapse

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: The high incidence of non-organ specific autoantibodies in patients with mitral valve prolapse (MVP) may suggest an association between MVP and autoimmune diseases. A higher incidence of MVP in patients with chronic lymphocytic thyroiditis and Graves' disease has been demonstrated in various studies. In particular, an increased incidence of MVP in patients with autoimmune thyroid disease characterized with hyperthyroidism may suggest an association between MVP and thyroid functions. To the best of our knowledge, there is a lack of literature regarding the evaluation of autoimmune thyroid diseases in patients with MVP. This study primarily aimed to evaluate the autoimmune thyroid disease using thyroid ultrasonography and autoimmune thyroid antibodies in patients with MVP.

Materials and Methods: Thyroid function tests, thyroid autoimmune antibodies, and thyroid ultrasonographic examination were evaluated in 30 patients with MVP (19 females and 11 males; mean age: 29.6±9.3 years) and 30 healthy volunteers (19 females and 11 males; mean age: 27.6±7.5 years).

Results: Two groups were similar in terms of demographical and clinical characteristics. Evaluation of the thyroid functions, autoimmune thyroid antibodies, and thyroid ultrasonography revealed no statistically significant difference between the study groups.

Conclusion: The results of the study suggest no association between MVP and autoimmune thyroid diseases. This requires further clarification with large-scaled studies.

Keywords: Autoimmune thyroid disease, autoimmune thyroid antibodies, MVP, ultrasonography

INTRODUCTION

Mitral valve prolapse (MVP) is characterized by the bulging of one or two mitral leaflets toward the left atrium during the left ventricular systole. It is the most important cause of isolated mitral regurgitation that requires surgery in developed countries (1). The main signs and symptoms related to MVP include chest pain, palpitations, dyspnea, dizziness, fatigue, nervousness, distress, and panic attacks. MVP is the most common valvular disease in the general population. The prevalence and frequency of MVP is 2%-4% (2).

Mitral valve prolapse (MVP) is common in young adults; thus, the evaluation of its pathogenesis requires attention. A close relationship between the thyroid and heart and the migration of both organs together during ontogenic development may explain the cardiovascular alterations in thyroid diseases (3, 4). In recent studies on autoimmune thyroid diseases, including Hashimoto thyroiditis and Graves' disease, MVP frequency has been found to be significantly increased (5, 6). This relationship has also been determined by non-organ specific antibodies. Moreover, there are studies suggesting that MVP is an autoimmune disease per se. MVP prevalence has been found to be increased in patients with systemic lupus erythematosus and scleroderma (7-11). In particular, an increased MVP incidence in patients with autoimmune thyroid disease characterized with hyperthyroidism led us to investigate the association between MVP and thyroid functions.

This study aimed to investigate the association between MVP and autoimmune thyroid disease and thyroid functions. Therefore, we first aimed to evaluate the patients who were diagnosed with MVP for the presence of autoimmune thyroid disease and thyroid functions, to compare them with healthy controls, and finally to determine MVP prevalence in patients with positive antibody. The data of this study will be used to highlight the possible association between MVP and autoimmune thyroid disease and also between MVP and thyroid functions.

MATERIALS and METHODS

This study was conducted between June 2008 and January 2011 at Ankara Atatürk Training and Research Hospital Cardiology Clinic. Thirty patients (19 females and 11 males; mean age: 29.6±9.3 years) with a MVP diagnosis according to the guidelines of the "American College of Cardiology/American Heart Association Committee on

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Management of Patients with Valvular Heart Disease" published in 2006 were enrolled in the study. Patients with congenital heart disease, a previous diagnosis of autoimmune thyroid disease, ischemic or rheumatic heart disease, serious left ventricular systolic dysfunction, and connective tissue disease (e.g., Marfan and Ehler-Danlos syndromes) were excluded. All patients were informed regarding the study procedure, and they gave a written informed consent. The control group included 30 healthy subjects similar to the patient group in terms of age and gender (19 females and 11 males; mean age: 27.6±7.5 years). This clinical study was approved by the Local Ethics Committee.

Measurement of hormone levels

Free T3, free T4, thyroid-stimulating hormone (TSH) levels, and antithyroid antibody (anti-TPO, TSH receptor antibody, and anti-thyroglobulin) levels of the control and patient groups were analyzed with an Elecsys 2010 analyzer using commercial kits (Cobas, Roche; Rothkreuz, Switzerland) for free T3, free T4, and TSH measurements. The ranges for 2.5-97.5th percentile for free T3, free T4, and TSH levels were 1.57-4.71 pg/mL, 0.85-1.78 ng/dL, and 0.4-4.0 mIU/mL, respectively. Patients were diagnosed as euthyroid, subclinically hypothyroid, subclinically hyperthyroid, or hyperthyroid according to their free T3, free T4, and TSH levels by endocrinologists.

Imaging of the thyroid gland

The ultrasonography of the thyroid glands of both the control and patient groups were evaluated. This analysis was performed at Ankara Atatürk Training and Research Hospital Radiology Clinic. The echogenicity of the gland, presence of nodules, paraglandular lymph nodes, and size of the gland were all evaluated.

Electrocardiogram (ECG)

Electrocardiogram (ECG) recordings were performed using 12-lead ECG (Nihon Kohden Corp) standardized to 10 m/mV and at a rate of 25 mm/h. The recordings were routinely analyzed in terms of rhythm, heart rate, QRS axis, PR interval, QRS width, P-wave amplitude, P-wave duration, QRS amplitude and R/S ratio, abnormal Q waves, and abnormalities of ST segment and T waves.

Echocardiography

Conventional echocardiographic imaging was performed by a single cardiologist using Vingmed System 7 (Vivid 7 Pro; Horton, Norway) via a 2.5-3.5 Hz transducer. Echocardiographic evaluation was performed in a left lateral decubitus position according to the recommendations of the "American Society of Echocardiography" (13). MVP diagnosis was defined as at least 2 mm posterior displacement of one or two leaflets of the mitral valve or posterior bulging of >3 mm during systole at M-mode echocardiography or superior displacement of one or two of the mitral valve leaflets >2 mm into the left atrium during systole in the parasternal or apical long-axis views with 2-D echocardiography (14). The cases were classified as either classical (primary) MVP (posterior displacement >2 mm and thickness >5 mm) or nonclassical (secondary) MVP (posterior displacement >2 mm and thickness <5 mm) (15). An increased leaflet thickness (>5 mm) and increased chorda and leaflets were observed in primary MVP. The degree of mitral regurgitation was assessed by color Doppler echocardiography as the ratio of the maximal regurgitant jet area to the area of the left atrium, color Doppler jet area, and jet length.

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows 11.5 (IBM SPSS Inc; Chicago, IL, USA).

Table 1. The demographic characteristics of subjects in the study groups

Variables	Control (n=30)	MVP (+) (n=30)	p value
Age	27.6±7.5	29.6±9.3	0.355
Male	11 (36.7%)	11 (36.7%)	
Body mass index	24.9±4.3	24.5±3.2	0.360
Hypertension	2 (6.7%)	2 (6.7%)	1.000
Diabetes mellitus	1 (3.3%)	1 (3.3%)	1.000

MVP: mitral valve prolapse

The distribution of the continuous variables was analyzed using Shapiro-Wilk test. Descriptive statistics for the continuous variables are presented as mean±standard deviation (SD) or median (minimum*maximum), and nominal variables are presented as n and percentages. Student's t-test and Mann-Whitney U test were used for the analysis of mean and median values, respectively. The nominal variables were analyzed using Pearson's chi square test or Fisher's exact test. A P value was considered significant when it is <0.05.

RESULTS

A total of 30 patients with MVP (19 females and 11 males; mean age: 29.6±9.3 years) and healthy volunteers (19 females and 11 males; mean age: 27.6±7.5 years) were enrolled in the study. The two groups were similar in terms of age, gender, body weight, body mass index, incidence of hypertension, and diabetes mellitus. The basal characteristics of the study groups were summarized in Table 1.

Twelve percent of patients with MVP who were diagnosed with echocardiography had classical MVP (40%), and the remaining 18 patients had secondary MVP (60%). The echocardiography data of patients were summarized in Table 2. There was no significant difference between the echocardiography data of the control group and patients with MVP.

Free T3, free T4, TSH, and thyroid autoantibody levels of the study groups were not significantly different. In both the groups, one subject had hyperthyroidism, one had hypothyroidism, and all others were euthyroid. Thyroid hormone and autoantibody values of the study subjects were summarized in Table 3.

Thyroid ultrasonographic data of patients with MVP and healthy controls were evaluated. The cases with abnormal ultrasonography results were further analyzed for the presence of thyroiditis and nodules. No statistically significant difference was observed between the two groups. The thyroid ultrasonography data were summarized in Table 4.

DISCUSSION

In this study, we investigated the incidence of autoimmune disease in patients with MVP using thyroid function tests, thyroid autoantibodies, and thyroid ultrasonography. There was no difference between the healthy control group and patients with MVP in terms of the thyroid function tests. Furthermore, we demonstrated for the first time that there is no difference between MVP and control groups in terms of autoimmune thyroid disease via thyroid autoantibodies and ultrasonography.

Table 2. The evaluation of the echocardiographic parameters of the subjects in study groups

Variables	Control (n=30)	MVP (+) (n=30)	p value
LVEDD (mm)	4.5±0.44	4.6±0.37	0.594
LVESD (mm)	2.5±0.2	2.4±0.24	0.929
LA (mm)	3.5±0.29	3.5±0.32	0.444
Peak mitral E (cm/s)	1.0±0.1	1.0±0.17	0.784
Peak mitral A (cm/s)	0.65±0.11	0.65±0.14	0.717
IVRT (ms)	74±14.5	76±15.4	0.780
IVCT (ms)	63.9±14.2	63.5±15.6	0.801
DT (ms)	191±38	185±36	0.108
EF (%)	64.7±2.3	65.5±1.4	0.290

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular systolic diameter; LA: left atrium; IVRT: isovolumic relaxation time; IVCT: isovolumic contraction time; DT: deceleration time; EF: ejection fraction; MVP: mitral valve prolapse

Table 3. The evaluation of the thyroid function tests and thyroid autoantibodies of the subjects in the study groups

Variables	Control (n=30)	MVP (+) (n=30)	p value
Hyperthyroidism	1 (3.3%)	1 (3.3%)	1.000
Hypothyroidism	1 (3.3%)	1 (3.3%)	1.000
Euthyroidism	28 (93.3%)	28 93.3%)	1.000
TSH (mIU/mL)	1.8 (0.1–10.5)	2.0 (0.9-11.2)	0.970
Free T3 (pg/mL)	3.1 (0.6–6.2)	3.1 (1.8-8.2)	0.959
Free T4 (ng/dL)	1.3 (0.3–3.4)	1.2 (0.2-4.6)	0.483
Anti-TPO positivity	2 (6.7%)	2 (6.7%)	1.000
Anti-TG positivity	2 (6.7%)	3 (10.0%)	1.000
TSH receptor antibody positivity	2 (6.7%)	2 (6.7%)	1.000

TSH: thyroid-stimulating hormone; MVP: mitral valve prolapse

Table 4. The evaluation of the thyroid ultrasonographic data of the subjects in the study groups

Variables	Control (n=30)	MVP (+) (n=30)	p value
Thyroiditis	2 (6.7%)	2 (6.7%)	1.00
Nodule	1 (3.3%)	1 (3.3%)	1.00

MVP: mitral valve prolapse

In recent studies on Hashimoto thyroiditis and Graves' disease, an increased incidence of MVP in these disease states (16-19) have been reported. A study by Evangelopoulos et al. (20) has shown a higher incidence of non-organ specific autoantibodies in patients with MVP compared with the healthy population and suggested that this association may be related to the autoimmune MVP origin. Brauman et al. (21) investigated MVP incidence in patients with Hashimoto thyroiditis and observed a 9.6-fold increase in MVP incidence in these patients in comparison with healthy population.

Thus, they concluded that patients with MVP may have a higher autoimmune disease incidence because both diseases have similar family characteristics and are associated with tissue antigens, including HLA-D3, BW35, and A3. In another study by Evangelopoulos et al. (20), the immunological parameters were investigated in patients with autoimmune thyroid diseases, and the association between MVP and autoimmune diseases (22). In 29 patients with Graves' disease, nine had MVP, whereas none of the controls had MVP ($p<0.05$). Antinuclear antibody data revealed a significant difference between MVP (+) and MVP (–) patients with Graves' disease ($p<0.05$). Moreover, there were significant differences between MVP (+) and MVP (-) patients with Graves' disease in terms of antiphospholipid antibodies, rheumatoid factor, and non-organ specific other antibodies ($p<0.05$), and this result led to the conclusion that MVP may be a disease with autoimmune origin.

In the light of these studies suggesting that MVP may be an autoimmune disease, we investigated the incidence of autoimmune thyroid disease in patients with MVP and the possible association between two diseases; however, no difference was observed between patients with MVP and healthy controls.

Serum TSH value is a sensitive test used for the diagnosis of both hyper and hypothyroidism (23). In patients with primary hypothyroidism, serum TSH level is >5 mIU/mL, and in patients with hyperthyroidism, it is <0.03 mIU/mL (24). In our study, serum TSH, free T3, free T4, anti-TPO, anti-TG, and TSH receptor antibody levels were evaluated in patients with MVP and controls, and all were evaluated with thyroid ultrasonography. No difference was observed between the two groups in terms of serum thyroid hormones and thyroid autoantibody levels.

Brauman et al. (25) investigated MVP incidence in patients with Graves' disease and hyperthyroidism due to toxic nodular goiter and found an increased MVP incidence in patients with hyperthyroidism due to Graves' disease. MVP incidence in patients with toxic nodular goiter was not found to be different compared with that in subjects of the control group, and similar to our study, they did not observe an increased hyperthyroidism incidence in patients with MVP (25).

Khoo et al. (12) have reported an increased MVP incidence in a Chinese family having TSH receptor gene mutation and suggested that TRSH receptor gene mutation may be associated with increased MVP incidence in people with genetic predisposition. In particular, they considered that an increased MVP incidence in autoimmune disease presenting thyrotoxicosis was related to the TSH receptor gene mutation. However, we did not observe a significant difference between patients with MVP and controls in terms of hyperthyroidism frequency and TSH receptor antibody positivity.

Alvarado et al. (26) investigated the association between MVP and Graves' disease considering thyroid functions. Their study enrolled 32 patients with Graves' disease (16 had hyperthyroidism and 16 had hypothyroidism or euthyroidism) and 40 healthy volunteers, and they observed a higher MVP incidence in patients with Graves' disease compared with controls; no significant difference between patients with Graves' disease having hyperthyroidism and those without hyperthyroidism in terms of MVP incidence. Thus, they indicated that MVP incidence was increased in patients with Graves'

disease independently of the thyroid function tests. In our study, we observed no difference between the control and MVP groups in terms of thyroid function tests. Thus, our study supported the notion that the association between MVP and autoimmune thyroid diseases is independent of the thyroid function tests.

Similar to our study, Türker et al. (27) compared patients having MVP with the control group in terms of thyroid function tests in a study in 2009 and found no significant difference between the two groups.

The most important limitation of our study is that the number of patients enrolled in the study is low. Thus, large-scaled studies are required to demonstrate that MVP is a disease with autoimmune origin and to reveal the possible association between MVP and thyroid function tests.

CONCLUSION

To the best of our knowledge, research on the incidence of autoimmune thyroid disease in patients with MVP using ultrasonography and thyroid antibodies is lacking in the literature. In this study, patients with MVP were compared with healthy controls in terms of thyroid function tests, thyroid antibodies, and thyroid ultrasonography data, and no significant difference was observed between the two groups.

In contrast to other studies investigating the association between MVP and autoimmune thyroid diseases, this study demonstrated no significant difference among patients with MVP in terms of increased autoimmune thyroid disease incidence and thyroid function tests.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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