Evaluation of thyroid function tests in patients with mitral valve prolapse

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Özet

Mitral valv prolapsuslu hastalarda tiroid fonksiyon testlerinin değerlendirilmesi

Amaç: Tiroid bezi ve kalbin embriyolojik olarak yakın bir ilişkisi vardır. Ontojenik gelişimde tiroid ve kalp birlikte göç ederler. Tiroid hastalıklarında meydana gelen kardiyovaküler fonksiyonlardaki değişikliklerin bu yakın ilişkiden dolayı kaynaklanabileceği düşünülmüştür. Kronik lenfositik tiroidit ve Graves hastalığında MVP insidansının arttığı fakat toksik nodüler guatrda anlamlı değişiklik olmadığı gösterilmiştir. Bilgimize göre Türkiye'de, MVP'li hastalarda tiroid fonksiyonlarının değerlendirildiği bir çalışma bulunmamaktadır. Bu çalışmanın temel amacı, mitral valv prolapsuslu (MVP) hastalarda tiroid fonksiyon testlerinin değerlendirilmesidir. Metod: Çalışmaya, mitral valv prolapsuslu ardışık 58 hasta (32'si kadın; yaş ortalaması 33±10, dağılım 16-68) ve kontrol grubu olarak sağlıklı asemptomatik 35 vaka (26'sı kadın; yaş ortalaması 38±11, dağılım 16-58) alındı. Her iki gruptaki tüm olguların tiroid fonksiyon testlerine bakıldı. Bulgular: Grupların bazal demografik ve klinik özellikleri benzerdi. İki grubun serbest serum triiyodotironin (sT3), serbest tiroksin (sT4) ve tiroid stimulan hormon (TSH) düzeyleri arasında anlamlı fark yoktu. Serum TSH düzeyleri, MVP grubundaki iki (%3) hastada normal sınırın altında iken, kontrol grubundaki tüm olgularda normal idi (p=0.272). Her iki gruptaki tüm hastaların serum serbest T3 ve serbest T4 düzeyleri normal sınırlar arasında idi. Sonuç: Çalışmamızın bulguları, MVP ile hipertiroidizm arasında bir ilişki olmadığını düşündürtmektedir. Bu konunun aydınlatılmasında büyük klinik çalışmalara ihtiyaç vardır.

Anahtar kelimeler: mitral valv prolapsusu, tiroid fonksiyon testi

Abstract

Objective: The thyroid gland and the heart share a close relationship arising in embryology. In ontogeny, the thyroid and heart anlage migrate together. The close physiological relationship is affirmed by predictable changes in cardiovascular function across the entire range of thyroid disease states. The prevalence of MVP is significantly elevated in Graves' disease and chronic lymphocytic thyroiditis, but not in toxic multinoduler goiter. No studies have previously evaluated thyroid function tests in patients with MVP in Turkey. The main objective of this study was to evaluate the thyroid function tests in patients with mitral valve prolapse (MVP). Methods: The study population consisted of 58 consecutive patients (32 women; mean age 33±10 years, range 16 to 68) with MVP and 35 asymptomatic healthy subjects the control group (26 woman; mean age 38±11 years, range 16 to 58). All the subjects in the two groups underwent thyroid function tests. Results: Baseline demographic and clinical characteristics of two groups were similar. There was no significant difference in the serum levels of free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) between the two groups. Serum TSH concentrations were under the lower limit of normal in 2 patients (3%) in the MVP group, however, they were within the normal limits in all the patients with control group (p=0.272). Serum fT3 and fT4 levels were within the normal range in the all patients in the both groups. Conclusion: This finding suggests that there is no relationship between the MVP and hyperthyroidism. Large clinical trials are required to clarify this issue.

Key words: mitral valve prolapse, thyroid function test

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Müracaat tarihi: 26.05.2009
Kabul tarihi: 09.12.2009

Introduction

Mitral valve prolapse (MVP) is the most common cardiac valvular abnormality in industrialized countries and the leading cause of mitral valve surgery for isolated mitral regurgitation (1,2). MVP is generally understood to be the systolic displacement of an abnormally thickened, redundant mitral leaflet into the left atrium during systole (3). Its prevalence has been estimated around 2.4%, ranging from 2% to 4% (4,5).

The thyroid gland and the heart share a close relationship arising in embryology. In ontogeny, the thyroid and heart anlage migrate together. The close physiological relationship is affirmed by predictable changes in cardiovascular function across the entire range of thyroid disease states (6-8).

The prevalence of MVP is significantly elevated in Graves' disease (9,10) and chronic lymphocytic thyroiditis (11,12), but not in toxic multinoduler goiter (13). Khoo et al. reported a family, in which activating thyroid stimulating hormone receptor (TSH-R) mutation is associated with MVP (14). No studies have previously evaluated thyroid function tests in patients with MVP in Turkey. The aim of this study was to evaluate the thyroid function tests in patients with MVP compared with control group.

Material Methods

Patients

A total of 65 consecutive patients with MVP were included in this study in our centre between October 2002 and January 2005. Exclusion criteria included ischaemic or rheumatic heart disease, severe left ventricular dysfunction, patients with Marfan syndrome and congenital heart disease. Of the 65 patients evaluated, 7 were excluded because of rheumatic heart disease (n=6) or Marfan syndrome (n=1). Therefore the population of this study consisted of 58 patients (32 women; mean age 33±10 years, range 16 to 68) with MVP and 35 asymptomatic healthy subjects the control group (26 woman; mean age 38±11 years, range 16 to 58).

Echocardiography

In all subjects, transthoracic two-dimensional and Doppler echocardiographic examinations were performed using a Vingmed System V echocardiographic system (General Electric Vingmed Ultrasound), using 2.5–3.5 MHz transducers. The echographic criteria included displacement of the leaflet edges, thickness and redundancy of the valve, and the diameter of the mitral annulus (15). The displacement of each leaflet was measured in the parasternal long-axis view above a line connecting the mid portions of the annular hinge points. The thickness of the mitral valve was measured by M mode recording. Each leaflet was measured, and maximal thickness was used for categorization. On the basis of prior clinical and prognostic studies, subjects were classified as having classic MVP (displacement >2 mm, thickness ?5 mm) or nonclassic MVP (displacement >2 mm, thickness <5 mm) (16). The sites of MVP were classified as prolapse of the anterior mitral leaflet (AML) and posterior mitral leaflet (PML) (21). The degree of mitral regurgitation was assessed as maximal regurgitant jet area/LA area ratio in the parasternal and apical long-axis and apical four-chamber views (17).

All the subjects in the two groups underwent thyroid function tests. Thyroid hormones (free thyroxine (fT_4), free triiodothyronine (fT_3) and TSH were measured by chemiluminesans methods (Immulite, DPC Biermann GmbH, Germany). The normal reference ranges for thyroid hormones were as follows: TSH, 0.4–5.0 μIU/ml; fT_4, 0.7–1.7 ng/dl; fT_3, 1.7–4.8 pg/ml. Clinical hyperthyroidism was diagnosed by elevated fT_3, fT_4 and TSH levels below 0.03 μIU/ml in combination with clinical symptoms (18).

Statistical analysis

Parametric values are expressed as mean±SD, nonparametric values are presented as percentages. The t-student test was used to compare the parametric values and X^2 was used to compare non-parametric values. A value of $p<0.05$ was considered significant.

Results

A total of 58 consecutive patients (32 woman; mean age 33±10 years, range 16 to 68) with MVP and the control group consisted of 35 normal individuals (26 woman; mean age 38±11 years, range 16 to 58) were included in this study. Baseline demographic and clinical characteristics of two groups were similar (Table 1).

Table 1 Demographic characteristics

Variable	MVP (n=58)	Control (n=35)	P Value
Age, year	33±10	38±11	0.28
Female gender (%)	32 (56)	26 (74)	0.20
Diabetes mellitus, n	1	1	0.41
Ejection fraction (%)	70±2.6	71±1.7	0.52
Hypertension, n	3	1	0.56

Values are mean+SD (range) or n (%).

Of the 58 patients with MVP detected by echocardiography, 44 (76%) had prolapse of the anterior leaflet, 4 (7%) had prolapse of the posterior leaflet and 10 (17%) had prolapse of both anterior and posterior leaflet. There were no cases of mitral chordal rupture. All patients had mitral regurgitation on color Doppler echocardiography. The mitral regurgitation was mild in 49 (85%), moderate in 7 (12%), and moderate to severe in 2 (3%). Echocardiographic data are detailed in Table 2. In relation to diastolic function, peak E, peak A, and the E/A ratio were not different in the two groups. Compared with controls, isovolumetric relaxation time was significantly higher in MVP patients (p=0.001).

Table 2. Echocardiographic data in controls and in patients with MVP

	MVP	Control	P Value
Left ventricular internal dimension at diastole (mm/m2)	47±4.5	45±3.3	0.08
Left ventricular internal dimension at systole (mm/m2)	30±3.5	28±3	0.30
Peak E (cm/sec)	0.93±0.2	0.88±1.6	0.11
Peak A (cm/sec)	0.64±0.17	0.63±0.16	0.67
E/A ratio	1.49±0.37	1.45±0.43	0.58
Deceleration time (msec)	185±36	183±38	0.53
Isovolumetric relaxation time (msec)	102±29	93±14	0.001
Ejection fraction (%)	70±2.6	71±1.7	0.25
Left atrial (mm)	34.5±4.7	35.8±3.1	0.03

There was no significant difference in the serum levels of fT_3, fT_4 and TSH between patients with MVP and controls group (Table 3).

Table 3. Laboratory characteristics

Variable	MVP	Control	P Value
Free $T3^{\gamma}$ (pg/ml)	3.2±0.5	3.2±0.4	0.07
Free $T4^{\varsigma}$ (ng/dl)	1.2±0.2	1.3±0.4	0.06
TSH^{τ} (µIU/ml)	1.6±1.2	2.0±1.9	0.27
Hyperthyroid	0	0	
Subclinic Hyperthyroid (%)	2 (3)	0	0.272
Euthyroid (%)	56 (97)	35	
Hypothyroidi	0	0	

$fT3_{\gamma}$: free triiodothyronine, $fT4_{\varsigma}$: free thyroxine, TSH_{τ}: thyroid stimulating hormone. Values are mean+SD (range) or n (%)

Serum fT3 (mean fT3 3.2±0.4 pg/m; range, 2,55-4.67 pg/ml), fT4 (mean fT4 1.3±0.4 ng/dl; range, 0.73-1.68 ng/dl) and TSH (mean TSH 2.0±1.9 µIU/ml; range, 0.52-4,37 µIU/ml) levels were within the normal range in the all patients of control group. Serum TSH concentrations (mean TSH 1.6±1.2 µIU/ml; range, 0.01-4.65 µIU/ml) were low in 2 patients (3%) in the MVP group and no patients in control group (p=0.272) (Table 3). Other serum concentration levels (mean fT3 3.2±0.5 pg/m; range, 1.79-4.36 pg/ml), fT4 (mean fT4 1.2±0.4 ng/dl; range, 0.72-1.57 ng/dl) were within normal range in patients with MVP.

Discussion

In the present study, we investigated the thyroid function test in 58 patients with MVP. There was no significant difference in the serum levels of fT_3, fT_4 and TSH between patients with MVP and controls group.

Channick et al surprisingly found a very high incidence of MVP in patients with hyperthyroidism due to Graves' disease (41% of 39 patients) (10). Brauman et al investigated the prevalence of MVP in patients with hyperthyroidism due to Graves' disease or toxic nodular goitre and that of hyperthyroidism in patients with MVP (13). The prevalence of MVP in the patients with toxic goiter was not significantly different from that in the controls. When the prevalence in the group with Graves' disease was compared with that in the control group the difference was significant. Only one patient with MVP had hyperthyroidism (13).

Serum TSH is the most widely used and most sensitive measure for the diagnosis of both hypothyroidism and hyperthyroidism (18). Serum TSH levels uniformly increase (>5 µIU/mL) in patients with primary hypothyroidism conversely the levels are low (<0.03 to 0.001 µIU/mL) in hyperthyroidism (6).

In patients with MVP some studies showed a higher prevalence of HLA-Bw35 (73% vs 39% in controls), but only in American black subjects (19). Another study, including predominantly white patients showed that the A3;Bw35 phenotype is quite specific for MVP (20). Autoimmunity is a well known causative factor in Graves' disease, (21) and recently it has been mentioned also in the etiology of MVP. Schlant et al., reported that 20 out of a total of 40 patients with MVP had a positive antinuclear factor compared with only 4% in a matched control group (22). In another study, patients with Graves' disease showed a significantly higher incidence of MVP (36/60, 60%) compared to the group with toxic nodular goitre (2/20, 10%) and to controls (238/2410, 9,9%) (p< 0.0001). Sixteen of 36 patients had a prolapse of the

anterior, in 3 of 36 the posterior leaflet was involved and 17 of 36 had both. In the same study, the authors remarked that thyroid function did not influence the incidence and intensity of the prolapse (23). Alvarado et al, determined the association between MVP and Graves' disease is related to thyroid function, three groups of individuals were studied: 16 patients with Graves' disease and hyperthyroidism, 16 patients with Graves' disease without hyperthyroidism, and 40 healthy individuals (24). They showed that, the frequency of MVP was similar in the hyperthyroid (31%) and euthyroid patients (25%), but was higher than in the normal individuals (5%) (24). They commented that, patients with Graves' disease have a higher frequency of mitral valve prolapse, this is not associated with thyroid function (24). Our study is in agreement with this study that there is no relationship between MVP and thyroid function tests. Reports of dilated cardiomyopathy associated with Graves' disease and evidence for TSH-receptors in the human myocardium suggest a relationship between these two diseases (25).

Evangelopoulou et al investigated the prevalence of MVP in patients with autoimmune thyroid disease and to evaluate whether any correlation between MVP and certain immunological parameters exists (26). Eight of 29 Graves' disease patients and 8 of 35 Hashimoto's thyroiditis patients had MVP, while none of the control group and 2 of 20 of the simple goiter group had MVP ($p < 0.05$). Antinuclear antibodies were detected at low titers in 5 of 8 in MVP (+) Graves' disease versus 3 of 21 in MVP(-) Graves' disease ($p < 0.05$). In the Hashimoto's thyroiditis group the MVP (+) patients had a significantly higher incidence of antinuclear antibodies and extractable nuclear antigen, 5 of 8 and 2 of 8 versus 5 of 27 and 0 of 27 of MVP(-) patients, respectively, $p < 0.05$. A statistically significant higher incidence of antiphospholipid antibodies was found in Hashimoto's thyroiditis MVP (+) patients (3/8) versus Hashimoto's thyroiditis MVP(-) 1/27, $p<0.05$. Rheumatoid factor levels (immunoglobulin A) were significantly higher in MVP(+) patients. The association of MVP with nonorgan-specific autoantibodies indicates that MVP may also be an autoimmune disease. They thought, it is possible that patients with autoimmune thyroid disease who also have MVP may be at an increased risk to develop systemic autoimmunity (26). Similarly, in another study antinuclear antibodies were detected in 17/75 in MVP patients versus 1/44 in the control group (27). In the MVP patients, thyroid autoantibodies, IgA and IgG RF were found at a statistically significant higher incidence, 16/75, 11/75 and 10/75 versus 1/44, 0/44 and 0/44 in the control group, respectively ($P < 0.05$). The levels of IgG anticardiolipin antibodies were significantly higher in the MVP(+) group, $P < 0.05$. They commented that, the presence of organ and non-organ specific autoantibodies in young healthy MVP(+) individuals insinuate the presence of subclinical autoimmunity and might suggest that autoimmune mechanisms might be involved in its pathogenesis (27). We have been unable to assess thyroid ultrasonography, antibodies to thyroglobulin and thyroperoxidase, organ and non-organ specific autoantibodies in our study sample. Any unmeasured potential factors might affect the results.

Study limitations

Sample size was small. We have been unable to assess thyroid ultrasonography, antibodies to thyroglobulin and thyroperoxidase for this study.

Conclusion

In conclusion, this finding suggests that there is no relationship between the MVP and hyperthyroidism. Large clinical trials are required to clarify this issue.

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