Hashimoto's Thyroiditis is a Frequent Occurrence in Patients with Rheumatic Mitral Stenosis

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Background and aim of the study: **Rheumatic mitral stenosis (RMS), an autoimmune sequel of streptococcal infection, causes significant morbidity and mortality. As Hashimoto's thyroiditis (HT) is recognized as the major form of chronic autoimmune thyroiditis, it was hypothesized that the coexistence of HT and RMS might have an autoimmune origin. The study aim was to examine this possible relationship.**
Methods: **A total of 55 consecutive patients with RMS was examined and compared to 54 healthy controls with normal echocardiographic findings. All subjects underwent transthoracic echocardiography and thyroid ultrasonography after a complete medical history and laboratory examination.**
Results: **The demographic data of the RMS group (38 females, 17 males; mean age 39.9 ± 9.3 years) and control group (39 females, 15 males; mean age 39.6 ± 10.5 years) were similar. HT was found to occur significantly more frequently in RMS patients (n = 16; 29%) than in controls (n = 6; 11%) (p = 0.019)**
Conclusion: **The higher frequency of HT in patients with RMS than controls may have genetic associations. Hence, further genetic-based studies should be conducted to provide a better understanding of this suggested relationship.**

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Rheumatic heart disease (RHD) is an autoimmune sequel of streptococcal infection complicated by acute rheumatic fever (ARF). Rheumatic mitral stenosis (RMS), which is frequently seen in developing countries and causes significant morbidity and mortality (1), is also known to be caused by ARF. Following the resolution of a streptococcal infection, activated autoreactive T cells react against the body's own tissues and organs, which leads to an autoimmune disease. Between 30% and 45% of children with ARF develop carditis, which in turn causes heart damage associated with pericardial, myocardial and endocardial involvement, followed by progressive and permanent valvular lesions leading to RHD (2).

Hashimoto's thyroiditis (HT), another autoimmune disease, is recognized as the major form of chronic autoimmune thyroiditis (3) and normally has symptoms of hypothyroidism. The condition is characterized by a diffuse goiter, together with a thyroid lymphocytic infiltrate and autoantibodies to thyroglobulin and thyroid peroxidase. It is very likely that cellular destruction in the thyroid gland is mediated by other cellular mechanisms, such as autoreactive T lymphocytes, natural killer cells and cytokines (4).

It was hypothesized that the coexistence of HT and RMS might have an autoimmune origin, as autoreactive T lymphocytes have a role in both diseases. The study aim was to examine the possible existence of this relationship.

Clinical material and methods

Patients

A total of 55 consecutive patients with RMS (38 females, 17 males; mean age 39.9 ± 9.3 years) and 54 healthy controls (39 females, 15 males; mean age 39.6 ± 10.5 years) was examined. The controls were selected from healthy subjects with normal echocardiographic findings. All patients and controls underwent transthoracic echocardiography and thyroid ultrasonography following a complete medical history and

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laboratory examination. Any patient receiving L-thyroxine, anti-thyroid medication, and those with diabetes mellitus, systemic autoimmune disease such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma, or with clinical or biochemical evidence of rheumatic activity was excluded.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol approved by the local ethics committee. All patients provided their written, informed consent to participate.

Laboratory measurements

Laboratory markers, which included thyroid hormone levels [thyroid-stimulating hormone (TSH), free triiodothyronine 3 (FT3), free triiodothyronine 4 (FT4)], anti-human thyroglobulin (HTG) and anti-thyroid peroxidase (TPO) autoantibodies, were monitored as described in recent guidelines (5).

All blood samples, collected by venipuncture, were centrifuged at 3000×g for 5 min to separate the plasma, using a Nüve® NF 800 centrifuge. FT3 (measurement range 1-20 pg/ml) and FT4 (range 0.1-10 ng/ml) were assayed in plasma using a chemiluminescence method (Diasorin, Liason®), while TSH (range 0.004-100 mIU/l), anti-TPO (range 1-2000 IU/ml) and anti-thyroglobulin (range 5-5000 IU/ml) were each monitored using a two-site immunoluminometric method (Diasorin, Liason).

A positive diagnosis of HT was confirmed by the presence of TPO and/or HTG antibodies, thyroid dysfunction and/or diffuse or nodular goiter, atrophic autoimmune thyroiditis without goiter but positive antibodies, and thyroid dysfunction (3).

Transthoracic echocardiography

Transthoracic echocardiography examinations were conducted in all subjects using a System 3 (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner fitted with 3.5 MHz transducers.

The left ventricular and left atrial dimensions were measured in the parasternal long-axis view, while left ventricular end-diastolic and end-systolic dimensions were measured using M-mode echocardiography. The aortic root diameter was measured using the parasternal long-axis view, and the left ventricular ejection fraction assessed using the Teichholz equation.

Mitral stenosis was diagnosed based on the echocardiographic detection of typical B-mode features from parasternal long-axis and apical four-chamber views; these included a thickening of the valve leaflets and chordal apparatus, restricted leaflet separation, diastolic doming of the anterior mitral leaflet, commissural fusion and upward movement of posterior mitral leaflet in early diastole. Mitral stenosis was quantified by planimetry of two-dimensional (2D) images and

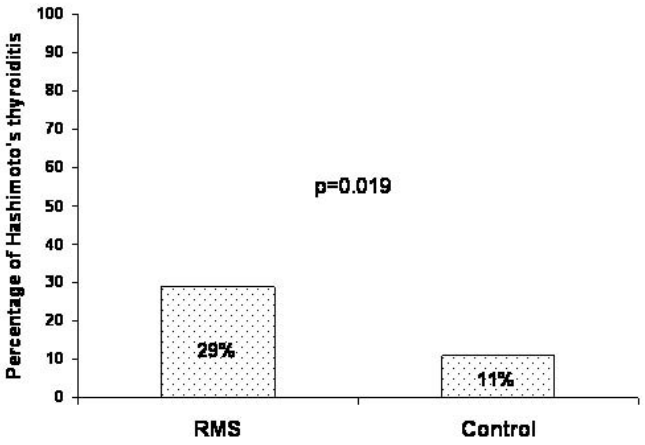

Figure 1: Frequency of Hashimoto's thyroiditis in patients with rheumatic mitral stenosis (RMS) and controls.

Doppler measurements of the transvalvular gradients. The mitral valve area (MVA) was measured using continuous-wave Doppler (pressure half-time method) and also 2D-echo planimetry.

Thyroid ultrasonography

Ultrasonographic examinations were performed using a LOGIQ 200 unit (General Electric Medical Systems, Milwaukee, WI, USA) attached to a broadband linear probe (5–12 MHz) with a 3.8 cm-wide field of view at a 4 cm depth of view. The ultrasonography studies were carried out in all subjects by a single physician, who was blinded to the laboratory findings. The ultrasonography study was performed with the patient in the supine position, with a cushion under the shoulders and the neck hyperextended. In order not to underestimate the vascularization intensity, the probe was lightly positioned on the skin, without any compression. The thyroid volume was calculated using the ellipsoid formula (6). The presence of hypoechoic and dyshomogeneous echogenicity was arbitrarily rated at three levels (0 = normal echogenicity; 1 = slightly hypoechoic and dyshomogeneous; and 2 = severely hypoechoic and dyshomogeneous) to evaluate structural abnormalities of the thyroid tissue associated with thyroid autoimmunity (7). The presence and numbers of thyroid nodules were recorded.

Statistical analysis

All data were reported as mean ± SD for normally distributed continuous variables, as median (minimum-maximum) for skew distributed continuous variables, and as frequencies for categorical variables. The Pearson chi-square test was performed for the comparison of categorical variables. Means of normal-

ly distributed continuous variables were compared by ANOVA. Skew-distributed continuous variables were compared using the Mann-Whitney *U*-test. The Statistical Package for Social Sciences (SPSS) for Windows version 10.0 (SPSS Inc., Chicago, USA) was used for the analysis, and a two-sided p-value <0.05 was considered to be statistically significant.

Results

The baseline characteristics of both groups are shown in Table I, and echocardiographic parameters in Table II. Among RMS patients the mean MVA was 1.62 ± 0.35 cm^2, while the peak and mean gradients were 14.52 ± 5.85 and 6.90 ± 3.83 mmHg, respectively.

Among RMS patients, thyroid ultrasonography demonstrated the presence of a solitary thyroid nodule in four cases (7%), multiple nodules in nine (16%), and no nodules in 42 (76%). Among control subjects, a solitary nodule was detected in three (6%), multiple nodules in eight (15%), and no nodules in 43 (80%). The thyroid volume did not differ significantly between the RMS and control groups (14.5 ± 6.0 ml and 14.7 ± 6.7 ml, respectively).

Hashimoto's thyroiditis was shown to occur significantly more often in RMS patients (n = 16; 29%) than in controls (n = 6; 11%) (p = 0.019; Fig. 1).

Discussion

To the present authors' knowledge, this study is the first to evaluate the frequency of HT among patients with RMS. In addition to the frequency of HT being greater among RMS patients than controls, the prevalence 3-10% was higher among those aged over 55 years of age and among females than reported previously (8). The prevalence among control subjects in the present study was 11%, and consistent with values reported elsewhere (9).

The pathogenesis of RHD appears to relate to an overt immune response involving either humoral or cellular reactions (or both), triggered by group A streptococci infection. Zabriskie et al. provided support to the hypothesis that ARF has an autoimmune origin by describing the presence of antibodies that were cross-reactive with streptococcal membrane antigens in ARF sera (10,11). Fae et al. reported a series of results showing T-cell immune responses that characterized RHD as a post-infectious autoimmune disease, fulfilling most of the major criteria for a molecular mimicry between streptococcal antigens and human proteins (12).

The link between autoimmune disease and the major histocompatibility complex-human leukocyte antigen (MHC-HLA) has long been known. Genetic polymorphism, and in turn structural variants of the MHC-HLA molecules on the surfaces of antigen-presenting cells, may increase susceptibility to certain autoimmune diseases due to their roles in the thymic selection of T cells and antigenic peptide presentation to peripheral T cells. Indeed, there is increasing evidence to suggest that the MHC-HLA gene regions play an important role in the development of HT, as they do in RMS (13,14).

MHC class II expression is normally not detected on thyroid cells, and its aberrant expression on thyrocytes is associated with autoimmune thyroid diseases. Aberrant MHC class II expression has been associated with multiple autoimmune diseases, an observation which led to the hypothesis that aberrant class II expression allowed cells to become antigen-presenting cells, to interact with T cells, and to initiate an immune response (15,16). Amoils et al. observed HLA-DR-positive fibroblasts in cardiac tissue obtained from patients with acute rheumatic fever, but fibroblasts expressing HLA-DR were not found in valves or myocardial tissue from normal individuals dying from trauma (17). Aberrant MHC class II expression in thyrocytes from patients with autoimmune thyroid disease, and in fibroblasts from the cardiac tissue of patients with acute rheumatic fever, may suggest a common pathogenetic mechanism for both diseases, and might also help to explain the present findings.

In previous investigations of the association of RHD with other autoimmune diseases, McCormack et al. demonstrated a link between ARF, a sequel of group A streptococcal infection with systemic lupus erythematosus or Sjögren's syndrome (18). Likewise, Todome

Table I: Demographic features and laboratory parameters of patients with and without rheumatic mitral stenosis (RMS).

Parameter	RMS (n = 55)	Controls (n = 54)	p-value
Age (years)*	39.9 ± 9.3	39.6 ± 10.5	NS
Gender ratio (M:F)	17:38	15:39	NS
FT3 (pmol/l)*	2.5 ± 0.6	2.5 ± 0.7	NS
FT4 (ng/dl)*	1.2 ± 0.3	1.1 ± 0.3	NS
TSH (μIU/ml)*	3.1 ± 1.3	3.0 ± 1.3	NS
Anti TPO (IU/ml)+	11.7 (1-78)	5.3 (0.5-55)	0.022
Anti Tg (IU/ml)+	23 (1.9-1955)	19 (2.3-162)	NS
HT (n)	16 (29)	6(11)	0.019

*Values are mean ± SD.
+Values are mean (range).
Values in parentheses are percentages.
FT3: Free triiodothyronine 3; FT4: Free triiodothyronine 4; HT: Hashimoto's thyroiditis; NS: Not significant; Tg: Thyroglobulin; TPO: Thyroid peroxidase; TSH: Thyroid-stimulating hormone.

Table II: Echocardiographic parameters of patients with and without rheumatic mitral stenosis (RMS).

Parameter	RMS (n = 55)	Controls (n = 54)	p-value
LVEDD (cm)	4.8 ± 0.5	4.7 ± 0.5	NS
LVESD (cm)	3.2 ± 0.6	3.0 ± 0.4	NS
LVEF (%)	61.8 ± 6.1	62.5 ± 5.0	NS
LAD (cm)	4.7 ± 0.9	3.3 ± 0.5	<0.001

Values are mean ± SD.
LAD: Left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end-systolic diameter; NS: Not significant.

et al. identified serum antibodies that were reactive with streptococcal cell wall peptidoglycan and its peptide subunit in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and acute rheumatic fever, compared with healthy subjects (19).

In conclusion, Hashimoto's thyroiditis occurs more frequently among patients with RMS than in controls, and genetic factors may be important in explaining this association. Further genetic studies may provide a better understanding of this relationship.

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