Interrelations Between Fibromyalgia, Thyroid Autoantibodies, and Depression

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ABSTRACT. ***Objective.*** To detect and quantify the association between fibromyalgia (FM) and thyroid autoimmunity.

Methods. This cross-sectional study comprised 146 women with FM and 74 case-controls, all 18 years of age or older. FM was diagnosed according to the American College of Rheumatology 1990 classification criteria. The Mini-International Neuropsychiatric Interview (MINI) was applied for the diagnosis of depression, previously considered as an important confounding factor. Thyroid autoimmunity was defined as the occurrence of detectable antithyroid peroxidase antibodies and/or antithyroglobulin antibodies by the immunometric assay. Cases of diffuse connective tissue diseases and thyroid dysfunctions (hypo or hyperthyroidism) were excluded in both groups.

Results. Univariate analysis detected an association between FM and thyroid autoimmunity (odds ratio, OR = 3.87, 95% confidence interval, CI = 1.54-10.13), depression (OR = 3.94, 95% CI = 1.97-7.93), and age (OR = 1.04, 95% CI = 1.01-1.07). In the final logistic regression model, after adjustment for depression and age, the association between FM and thyroid autoimmunity was strengthened (OR = 4.52, 95% CI = 1.86-11.0).

Conclusion. Our results suggest an association between FM and thyroid autoimmunity. (J Rheumatol 2004;31:2036–40)

Key Indexing Terms:
FIBROMYALGIA AUTOIMMUNITY THYROID GLAND DEPRESSION

Fibromyalgia (FM) can be defined as a non-inflammatory chronic painful syndrome characterized by widespread musculoskeletal pain and the presence of tender points[1]. Most patients have the typical symptoms of sleep disturbances (non-refreshing sleep), fatigue, and morning stiffness. Other symptoms, such as headaches, paresthesias, depression, anxiety, irritable colon syndrome, female urethral syndrome, sicca symptoms, and Raynaud's phenomenon are also present[2-6].

It is a common rheumatic disorder, affecting an estimated 3.7 million people in the United States. Prevalence is greater in women (3.4%) than in men (0.5%). Overall prevalence for persons age 18 and older is approximately 2.0% and increases with age[7]. The prevalence of FM in Brazil is still unknown.

The cause of FM has not been defined, but associations between the syndrome and physical injury, psychological distress, some infections, and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus have been reported[8-18].

Depression is prevalent in a large proportion of patients with FM, ranging from 14.0 to 71.0% in different studies. This may be attributed to variability in sample selections and differences in criteria used to identify depression in most studies. However, the prevalence of depression in FM exceeds that of the healthy population in developed countries, estimated as 2.7% to 4.6% for men and 4.6% to 6.5% for women[19]. In fact, depression is relatively common in several diseases and chronic clinical conditions and therefore not specific to FM[20].

Rheumatic complaints in patients with thyroid pathology have long been noted[21-25]. Becker, *et al*[25], in 1963, reviewed 506 patients with Hashimoto's thyroiditis and identified a secondary fibrositis syndrome in 40 (7.9%) of them. Aarflot and Bruusgaard[26] evaluated the association between chronic widespread complaints and thyroid autoimmunity. The authors reported a prevalence of thyroid antibodies that was higher in persons with than without musculoskeletal pain. This difference was restricted to women, and there were no differences related to thyroid function between the groups.

Several clinical signs and symptoms of thyroid dysfunction are similar to depression, and it is also true that depression may result in underlying hypothyroidism[27-29]. Transient postpartum thyroid dysfunction associated with autoimmune thyroiditis was first reported in 1976 by Amino, *et al*[28]. In 1998, Pop, *et al*[29] examined the relationship between autoimmune thyroid disease and depression in peri-

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Submitted August 28, 2003; revision accepted April 7, 2004.

menopausal women. The authors concluded that women with elevated antithyroid peroxidase antibodies (TPOAb) are especially vulnerable to depression, independent of postmenopausal status.

To test the hypothesis derived from observations in clinical rheumatology and supported by literature review, we conducted a cross-sectional study with case-control characteristics to evaluate the possible association between FM and thyroid autoimmunity. Depression was considered an important confounding factor, since it is associated with both FM and thyroid autoimmunity.

MATERIALS AND METHODS

Study population. The rheumatology outpatient clinic of Governador Israel Pinheiro Hospital, Belo Horizonte, is a referral center for the treatment of rheumatic diseases of the civil public servants in the state of Minas Gerais, Brazil. Currently, the estimated number of civil public servants is about 2.5 million in Minas Gerais.

Cases were defined as women aged 18 years or older who fulfilled the American College of Rheumatology (ACR) 1990 classification criteria for FM[30]. These classification criteria were validated for the Brazilian population in 1999[31]. Non-cases were defined as women aged 18 years or older who did not meet the ACR criteria. From both groups we excluded all patients with concurrent diagnosis of diffuse connective tissue disease and thyroid dysfunction, such as hypo or hyperthyroidism, and those who did not agree to participate in the study.

The study period lasted from August to December 2001. Cases and non-cases were both selected from the rheumatology outpatient clinic of the hospital and we assumed that they were representative of the same base experience[32,33].

Assuming an exposure prevalence for the occurrence of thyroid autoantibodies in healthy individuals ranging from 10.0 to 30.0%[34], the final sample was composed of 220 participants, 146 with FM and 74 without (2 cases to each non-case), with a 0.05 level of significance and a power of 80.0% to detect an odds ratio (OR) of 2.4 or greater.

The study was approved by the Ethics Committee of the Governador Israel Pinheiro Hospital. All participants gave their written consent after receiving and understanding information about the study.

Variables. The dependent variable was FM (present/absent). The main independent variable was thyroid autoimmunity.

Thyroid autoimmunity was defined as the occurrence of detectable TPOAb and/or antithyroglobulin antibodies (TgAb) by immunometric assay (reference ranges ≥ 35 IU/ml for TPOAb and ≥ to 40 IU/ml for TgAb) according to the manufacturer's instructions (IMMULITE® 2000, EURO/DPC Ltd, UK). Otherwise, thyroid autoimmunity was defined as absent.

Depression was diagnosed by the Mini-International Neuropsychiatric Interview (MINI)[35,36], a short (15-30 minutes) structured diagnostic interview compatible with the Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R), the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and the International Classification of Diseases (ICD-10) criteria[37-39]. Clinicians are able to use it after a short training (1-3 hours). The MINI DSM-IV 5.0 is available in almost 30 languages, including a Portuguese version[36]. The term depression was used to denote current major depressive disorder (present/absent).

For the reliability test the MINI was applied to 10% of the sample by the researcher and a psychiatrist giving a kappa statistic of 0.44, which was considered reasonable[40].

For the diagnosis of FM, tender points were evaluated by manual palpation, at a pressure of about 4 kg, of the 18 tender points considered.

The sociodemographic variables considered comprised age in years, race (white and non-white), marital status (married or non-married), education in years of schooling (< 9 or ≥ 9 years), and monthly family income in minimum wage units (< 5 or ≥ 5).

Data analysis. OR were used to quantify the magnitude of the associations[41-48]. Categorical data (e.g., thyroid autoimmunity, depression) were analyzed using chi-square and Mantel-Haenzel odds ratio (ORMH), and continuous data (e.g., age in years) were analyzed using Student's t test. The only continuous variable was age, except when it was dichotomized for multivariate analyses. Reliability analysis was performed with kappa statistics[40].

FM was cross-tabulated according to potential risk factors. The magnitude of associations was assessed along with confidence intervals (95% CI). Multivariate analysis was assessed by logistic regression. The models were compared using the likelihood chi-square. The final model goodness of fit was assessed by the Hosmer-Lemeshow test[49].

Epi Info 6.04 and Stata® Statistical Software 7.0 were used for data analysis[50,51].

RESULTS

In the FM group, widespread pain duration ranged from 6 months to 40 years (mean duration 9 years).

In the non-FM group, the musculoskeletal disorders were osteoarthritis (n = 50) and soft-tissue rheumatism (n = 20). Four participants had no detectable rheumatic disease.

As is shown in Table 1, cases and non-cases were comparable with respect to race, marital status, education, and monthly family income. However, the non-cases were older.

Table 2 summarizes the OR of the univariate and multivariate analyses. In the univariate analysis we found an association between FM and thyroid autoimmunity (OR = 3.87, 95% CI 1.54-10.13), depression (OR = 3.94, 95% CI 1.97-7.93), and age in years (OR = 1.04, 95% CI 1.01-1.07).

Despite the lack of association between depression and thyroid autoimmunity (p = 0.87), we investigated the association between FM and thyroid autoimmunity adjusting for depression (ORMH = 4.15, 95% CI 1.73-9.91) and age dichotomized by the median (OR = 3.91, 95% CI 1.65-9.22). The Breslow-Day test of homogeneity did not indicate interactions beyond stratum-specific OR.

The independent effects of thyroid autoimmunity, depression, and age in years were assessed through logistic regression modeling. The inclusion age strengthened the association between FM and thyroid autoimmunity (OR = 4.52, 95% CI 1.86-11.0). The association with depression was smaller (OR = 3.64, 95% CI 1.85-7.14) due to possible confounding. Goodness of fit was assessed by the Hosmer-Lemeshow with 2 degrees of freedom (p = 0.384).

DISCUSSION

Our results suggest an association between thyroid autoimmunity and FM, possibly as a determinant factor among several others considered for the risk of the syndrome[8–17,52,53]. Our study corroborates previous investigations about associations between thyroid autoimmunity and chronic musculoskeletal pain[25,26], although in these studies FM was not considered the main event.

A relevant aspect of this study was concern for the

Table 1. Frequency distribution of selected variables for cases and non-cases.

Variable	Cases, n = 146 (%)	Non-Cases, n = 74 (%)	p*	OR (95% CI)
Age, yrs, mean (range)	54.63 (29–78)	59.29 (32–78)	0.003	
Race**				
White	107 (73.8)	58 (80.6)	0.272	1.00
Non-white	38 (26.2)	14 (19.4)		0.68 (0.32–1.42)
Marital status**				
Married	74 (51.0)	36 (49.3)	0.06	1.00
Unmarried	71 (49.0)	37 (50.7)		1.21 (0.99–1.49)
Education**				
< 9 yrs	64 (46.0)	27 (37.5)	0.23	1.00
≥ 9 yrs	75 (54.0)	45 (62.5)		1.13 (0.93–1.36)
Monthly family income**				
< 5 minimum wages	75 (52.9)	41 (60.3)	0.35	1.00
≥ 5 minimum wages	65 (47.1)	27 (39.7)		0.92 (0.76–1.10)

* p value, chi-square test; ** missing values (1 for white and 2 for non-white; 1 for married and 1 for unmarried; education: 7 for < 9 years and 2 for ≥ 9 years of schooling and monthly income: 6 for < 5 and 5 for ≥ 5 minimum wage). One minimum wage unit equals about US$90.00.

Table 2. Results for univariate regression analysis and 2 different multivariate logistic regression analyses (models 1 and 2) with FM as the dependant variable.

Variable	OR	95% CI
Univariate		
Thyroid autoimmunity		
Absent	1.00	
Present	3.87	1.54–10.13
Depression		
No	1.00	
Yes	3.94	1.97–7.93
Age, yrs	1.04	1.01–1.07
Model 1		
Thyroid autoimmunity		
Absent	1.00	
Present	4.38	1.81–10.60
Depression		
No	1.00	
Yes	4.27	2.21–8.25
Model 2		
Thyroid autoimmunity		
Absent	1.00	
Present	4.52	1.86–11.00
Depression		
No	1.00	
Yes	3.64	1.85–7.14
Age, yrs	1.03	1.00–1.06

control of confounding factors such as depression and the exclusion of thyroid dysfunction and autoimmune disorders (e.g., diffuse connective tissue diseases). We are unaware of similar studies.

Depression and age are also associated with FM. In our study population, the prevalence of depression according to the MINI was high for both cases and non-cases. Depression was present in 52.0% of the cases, 27.0% of non-cases, and 42.0% of cases and non-cases. These prevalence rates were in accordance with literature for the FM group[19,20]. However, the prevalence for non-cases was higher than the prevalence for non-FM populations in developed countries and in Brazil[20,54]. This might reflect the characteristics of the study population, all of whom were attending a rheumatology outpatient clinic with high prevalence of pain as the main referred symptom.

The decision for adjustment came from statistical evidence (magnitude of the association for depression in the univariate analysis) and from biological and epidemiological premises (for both depression and age). Evidence for confounding was detected when the distribution of depression in non-exposed cases was different from its distribution among the non-exposed non-cases (p = 0.0004), reinforcing the concept of additive effects[55]. Other evidence included the 10.0% increase in the OR of the association between FM and thyroid autoimmunity after adjustment for depression[56].

The inclusion of age in the logistic regression model strengthened the magnitude of association between FM and thyroid autoimmunity, suggesting the possible confounding effect of depression. This model was considered the final one.

There are a number of limitations in our study that should be mentioned. The measurement of depression was conducted by one author (LSR), a rheumatologist without formal training in psychiatry. Despite all training and reliability testing, some degree of measurement bias may have occurred. Also, the observer was aware of the participants' FM diagnosis.

Other limitations of our study are sample size and study design. The greatest difficulty in selecting subjects for the study arose in the non-case group. The study population was recruited from a rheumatology outpatient clinic, and the exclusion criteria restricted the eligibility of many subjects and so influenced sample size. In a cross-sectional study, exposure and disease status are measured at one time or over

a short period of time. We did not intend to define directionality or temporality; however, the strength of the biological associations could be inferred with some confidence.

Internal validity was presumed by the fact that in the sample selection period, all the subjects considered eligible were included in the study with a minimum of losses. The demographic characteristics of the sample are according to the civil public servants profile (personal communication).

Depression and age were also found to be associated with FM, and depression turned out to be a confounder. Thus, one should be aware of its possible position in FM treatment planning, even though the treatment of FM is not the scope of this article.

In summary, our results suggest an association between FM and thyroid autoimmunity, and reinforce the associations identified with chronic musculoskeletal pain and the occurrence of thyroid antibodies.

Studies with larger samples and other determinants, such as physical injuries, infection markers, and genetic profile should be carried out to better understand the incidence and prevalence of FM.

ACKNOWLEDGMENT

The authors are grateful to the physicians in the Psychiatry Department of the Governador Israel Pinheiro Hospital for technical support and training with the MINI.

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