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ORIGINAL ARTICLE

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Thyroid hormones and thyroid-stimulating hormone in Egyptian patients with systemic lupus erythematosus: correlation between secondary hypothyroidism and neuropsychiatric systemic lupus erythematosus syndromes

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Abstract The purpose of this study was to determine the serum levels of thyroid hormones and thyroid-stimulating hormone (TSH), in addition to antithyroglobulin and antimicrosomal antibodies and to investigate the correlation between these hormones and various disease manifestations among Egyptian patients with systemic lupus erythematosus (SLE). A group of 45 patients with SLE (43 women and 2 men with a mean age of 27.57 ± 9.89 years) underment assessment of their thyroid hormones. Antithyroglobulin and antimicrosomal antibodies were assessed in 27 patients. Various disease manifestations were evaluated. A group of 20 normal female volunteers were involved as controls. The mean serum free triiodothyronine (FT_3) levels in all patients were significantly lower than in controls (1.89 ± 1.14 vs. 3.15 ± 0.93 pg/ml; $P < 0.05$). Patients with a history of intravenous pulsed cyclophosphamide therapy showed significantly decreased levels of FT_3 compared to those in other patients (1.17 ± 0.5 vs. 2.05 ± 0.95 pg/ml; $P = 0.04$). The mean serum free thyroxine (FT_4) levels in all patients were significantly less than in the control group (1.24 ± 1.22 vs. 1.4 ± 0.3 mg/dl; $P < 0.001$). Of the 45 patients, 2 (4.4%) were considered to have primary hypothyroidism. Five of six patients (83.3%) with decreased FT_4 levels developed fibromyalgia compared to 7 of 39 (17.9%) patients with normal T_4 ($P = 0.003$). The mean serum TSH levels in all patients were significantly higher than in the controls (4.82 ± 22.2 vs. 2.65 ± 1.18 μIU/ml; $P < 0.001$). Six patients with decreased TSH levels were considered to have secondary hypothyroidism (13.3%); one of them showed decreased T_3 and T_4, two had decreased T_4 only, and the other three were euthyroid. Comparing patients with and without secondary hypothyroidism, showed acute confusion in four (66.7%) in the former group versus four (10.3%) in the latter group ($P = 0.006$), anxiety in four (66.7%) in the former group versus six (15.4%) in the latter group ($P = 0.016$), and cognitive disorders in five (83.3%) in the former group versus nine (23.1%) in the latter group ($P = 0.008$).

This study demonstrated evidence of secondary as well as primary hypothyroidism in SLE patients and revealed a close association between thyroid hormones or TSH and some organ involvement in SLE.

Key words Fibromyalgia · Jaccoud's arthropathy · Neuropsychiatric systemic lupus erythematosus (SLE) syndromes · Systemic lupus erythematosus (SLE) · Thyroid hormones · Thyroid-stimulating hormone (TSH)

Introduction

Autoimmune thyroid disorders have been shown to occur more frequently than suspected in patients with connective tissue diseases. Abnormal thyroid function test results are common in patients with systemic lupus erythematosus (SLE).[1] Hypothyroidism and thyrotoxicosis have been recognized in SLE. Moreover, a high prevalence of antithyroid antibodies has been found in those patients.[2] The aim of this study was to estimate thyroid hormones and thyroid-stimulating hormone (TSH) in a group of Egyptian SLE patients and then correlate the prevalence of function test results with the laboratory indices or disease manifestations and with the presence of antithyroid antibodies.

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Patients and methods

Patients

A group of 45 nonsmoking patients affected by SLE were studied. There were 43 women and 2 men with a mean age of 27.57 ± 9.89 years (range 15–55 years); the mean duration of SLE was 4.86 ± 6.59 years (range 0.5–38.0 years); and the mean age of onset was 22.2 ± 9.26 years (range 4–51 years). They all attended the Department of Rheumatology and Rehabilitation, Kasr Eleini Hospital, Cairo University and fulfilled the American College of Rheumatology (ACR) criteria for a diagnosis of SLE.[3] They were evaluated for free triido thyronine (FT_3), free thyroxine (FT_4), and TSH. None was known to have any thyroid abnormality. Antithyroglobulin and antimicrosomal antibodies were assessed in 27 patients. Thyroid ultrasonography was used in patients with abnormal thyroid functions. Twenty normal volunteers (mean age 28.9 ± 15.9 years) served as controls for thyroid hormone, TSH, and autoantibody measurements. Written documents of agreement were obtained from all patients and controls.

All patients underwent a complete clinical examination including evaluation for gastrointestinal, pulmonary, cardiac, renal, articular, muscular, and neurological involvement. Neuropsychiatric SLE syndromes were defined using the 1999 ACR nomenclature.[4] The Mini-Mental State Examination was used to assess the patients' cognitive status.[5] Fibromyalgia was diagnosed according to the 1990 ACR criteria.[6] The SLE activity measurement score (SLAM) was used to assess disease activity.

Routine laboratory examinations included a complete blood picture, erythrocyte sedimentation rate (ESR), liver and kidney function assessment, and creatinine phosphokinase (CPK) level. Autoimmune profiles were obtained, including antinuclear antibodies (ANA) by immunofluorescence, anti-DNA, and complements 3 and 4 for all patients. Computed tomography (CT), standard magnetic resonance imaging (MRI), angiography, electroencephalography, echocardiography, and the antiphospholipid antibody assay were used when needed.

Quantitative determination of FT_3 and FT_4 for all patients and controls was done by radioimmunoassay using Coat-A-Count Free T_3 and Free T_4 (DPC, Los Angeles, CA, USA). Normal ranges (mean of the controls ± 2 SD) were for FT_3 1.3–5.0 pg/ml and for FT_4 0.8–2.0 ng/dl. Quantitative determination of TSH for the patients with abnormal thyroid hormones was done by immunoassay using the Coat-A-Count TSH IRMA (DPC). The normal range for TSH was 0.3–5.0 μIU/ml. Antithyroglobulins and antimicrosomal antibodies were screened for and semiquantitatively determined by an indirect immunofluorescence test system using NOVA Lite thyroid–anti-thyroid antibody (INOVA Diagnostics, San Diego, CA, USA).

Table 1. General features and thyroid hormone levels of all patients, patients with secondary hypothyroidism (group A), and patients without secondary hypothyroidism (group B)

Parameter	All patients (n = 45)	Group A (n = 6)	Group B (n = 39)
Age (years)	27.6 ± 9.9	26.7 ± 9.5	27.7 ± 10.2
Age of onset (years)	22.2 ± 9.3	21.3 ± 11.2	22.3 ± 9.1
Disease duration (years)	4.9 ± 6.6	5.3 ± 5.6	4.8 ± 6.8
FT_3 (pg/ml)	1.9 ± 1.1	1.7 ± 0.5	1.9 ± 1.2
FT_4 (ng/dl)	1.2 ± 1.2	0.8 ± 0.19	1.3 ± 1.3
TSH (μIU/ml)	4.8 ± 22.2	0.1 ± 0.07	5.5 ± 23.8

Student's t-test was used to determine significance. There were no significant differences between groups for any of the parameters
FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid-stimulating hormone

Statistical analysis

Data were reported as the mean ± standard deviation. Student's t-test, chi-square test with Fisher's exact test, and Yates correction were used when appropriate. Correlation analysis was performed utilizing Pearson's correlation. Correlation between continuous variables were evaluated by linear regression analysis.

Results

The general features of all patients are shown in Tables 1 and 2.

Serum FT_3 and FT_4 levels and correlation with disease manifestations

The mean serum FT_3 level in all patients was significantly lower than in controls (1.89 ± 1.14 vs. 3.15 ± 0.93 pg/ml; $P < 0.05$). One in ten with decreased FT_3 levels was considered to have a decreased T_3 level secondary to decreased TSH (1/45, 2.2%), and two were judged to have primary T_3 decreased levels with increased TSH (2/45, 4.4%).

Thyroid dysfunction was diagnosed based on thyroid function evaluations, except for the patient with hyperthyroidism who presented with thyroid swelling. Patients with a history of intravenous pulsed cyclophosphamide showed significantly decreased T_3 levels compared to other patients (1.17 ± 0.5 vs. 2.05 ± 0.95 pg/ml (P = 0.04). The mean serum FT_4 levels in all patients were significantly less than in controls (1.24 ± 1.22 vs. 1.4 ± 0.3 ng/dl; $P < 0.001$). Three of six patients with decreased T_4 were believed to have secondary T_4 hypothyroidism (3/45, 6.7%) and two to have the primary type (2/45, 4.4%).

Fibromyalgia was found in 12 of 45 (26.7%) patients in our study, with a mean of 13.25 ± 1.25 tender points. Five of six patients (83.3%) with T_4 hypothyroidism developed fibromyalgia compared to 7 of 32 (21.9%) patients with normal T_4 (P = 0.003). There were significantly more mean tender points in patients with T_4 hypothyroidism than in patients with normal T_4 (10.8 ± 5.4 vs. 4.14 ± 5.2; P = 0.01).

One patient presented with T_3 and T_4 thyrotoxicosis with decreased TSH levels (1/45, 2.2%) and positive

Table 2. Clinical manifestations of all patients, patients with secondary hypothyroidism (group A), and patients without secondary hypothyroidism (group B)

Clinical Manifestation	All patients (n = 45)	Group A (n = 6)	Group B (n = 39)	P
Malar rash (%)	30 (66.7)	5 (83.3)	25 (64.1)	NS
Discoid rash (%)	9 (20.0)	2 (33.3)	7 (17.9)	NS
Photosensitivity (%)	30 (66.7)	4 (66.7)	26 (66.7)	NS
Oral ulcers (%)	28 (62.2)	5 (83.3)	23 (58.9)	NS
Jaccoud's arthropathy (%)	6 (13.3)	2 (33.3)	4 (10.3)	NS
Serositis (%)	11 (24.4)	2 (33.3)	9 (23.1)	NS
Systemic hypertension (%)	14 (31.1)	2 (33.3)	12 (30.8)	NS
Myositis (%)	3 (6.7)	0	3 (7.7)	NS
Renal disease (%)	23 (51.1)	2 (33.3)	21 (53.9)	NS
Aseptic meningitis (%)	0	0	0	NS
Cerebrovascular disease (%)	1 (2.2)	0	1 (2.6)	NS
Headache (%)	18 (40.0)	6 (100)	12 (30.8)	0.019
Chorea (%)	1 (2.2)	0	1 (2.6)	NS
Seizure (%)	4 (8.9)	2 (33.3)	2 (5.1)	NS
Acute confusion (%)	8 (17.8)	4 (66.7)	4 (10.3)	0.006
Anxiety (%)	10 (22.2)	4 (66.7)	6 (15.4)	0.016
Cognitive disorders (%)	14 (31.1)	5 (83.3)	9 (23.1)	0.008
Mood changes (%)	21 (46.7)	6 (100)	15 (38.5)	0.03 NS[a]
Psychosis (%)	2 (4.4)	0	2 (5.1)	NS
Peripheral neuritis (%)	6 (13.3)	2 (33.3)	4 (10.3)	NS
SLAM score range (median)	4–17 (10.0)	7–17 (10.5)	4–17 (10.0)	NS
Steroids (%)	35 (77.8)	3 (50.0)	32 (82.1)	NS
Azathioprine (%)	20 (44.4)	3 (50.0)	17 (43.6)	NS
Cyclophosphamide (%)	15 (33.3)	0	15 (38.5)	0.027
Antimalarials (%)	26 (57.8)	4 (66.7)	22 (56.4)	NS

The chi-square test with Fisher's exact test and Yates correction were used
[a] Fisher's exact tests: 0.03 (one-tailed) but NS (two-tailed)

antithyroglobulin antibodies. Thyroid ultrasonography of patients with altered thyroid function revealed normal findings in all of them except the patient with T_3/T_4 thyrotoxicosis who exhibited a solitary solid thyroid nodule.

Serum TSH levels and correlation with disease manifestations

The mean serum TSH level for all patients was significantly higher than that of the controls (4.82 ± 22.2 vs. 2.65 ± 1.18 μIU/ml; $P < 0.001$). Two patients had elevated TSH levels with evidence of primary hypothyroidism (2/45, 4.4%). Seven patients (7/45, 15.6%) had decreased TSH levels, one with evidence of primary hyperthyroidism (2.2%). The other six patients with decreased TSH levels were believed to have secondary hypothyroidism (13.3%); one had decreased T_3 and T_4, two had decreased T_4 only, and the other three were euthyroid.

Comparing patients with and without secondary hypothyroidism showed acute confusion in four (66.7%) in the former group versus four (10.3%) in the latter group ($P = 0.006$), anxiety in four (66.7%) versus 6 (15.4%) ($P = 0.016$), and cognitive disorders in five (83.3%) versus 9 (23.1%) ($P = 0.008$).

Magnetic resonance imaging studies on patients with secondary hypothyroidism revealed normal findings. The general features, clinical manifestations, and thyroid hormones levels of patients with and without secondary hypothyroidism are compared in Tables 1 and 2. Comparison of the two groups concerning laboratory findings including an autoimmune profile revealed no significant differences between the groups (data not shown).

Antithyroglobulin and antimicrosomal antibodies

Antithyroglobulins were detected in 5 of 27 (18.5) patients compared to none in the control group (P = NS). Antimicrosomal antibodies were detected in 25 of 27 (95.6%) patients compared to 2 of 20 (10%) of the control group ($P = 0.0001$). Three of five patients (60%) with positive antithyroglobulin antibodies had a hand deformity (Jaccoud's arthropathy) compared to 3 of the other 40 patients 3/40 (7.5%) ($P = 0.01$).

Discussion

Hypothyroidism and thyrotoxicosis have been recognized in patients with SLE.[2] Our study revealed thyroid gland function abnormalities among Egyptians similar to those reported in previous studies.[7–10] The diagnosis of thyroid dysfunction in SLE patients may present some difficulty because of the similarity of the general manifestations of the two conditions. Antithyroglobulin and antimicrosomal antibody prevalence in our group was similar to that seen in previously reported studies.[2,11]

Although a low T_3 and T_4 state may develop in patients with nonthyroidal illness (low-T_3 syndrome), altered thyroid function associated with an altered TSH level has been

suggested to depend on the activity of the systemic autoimmune process.[2] Moreover, a correlation of altered thyroid function and the presence of antithyroglobulin and antimicrosomal antibodies has been described.[2,7–9,11,12]

Elevated TSH levels were correlated with positive antithyroglobulin assays and evidence of a mild, clinically silent primary hypothyroidism.[11] In the present study, evidence of secondary hypothyroidism was detected in 13.3% of patients, and a significant correlation with neuropsychiatric manifestations was found. This suggests that hypophyseal suppression may be a factor inducing altered thyroid function in patients with SLE in addition to the previously described factors. MRI was normal in those patients, and autoantibodies raised against the hypothalamus/pituitary gland were not detected.

Antirheumatic drugs, particularly glucocorticoids, may induce clinical abnormalities related to the thyroid gland, including depressed serum total T_3 and T_4 values; the clinical distinction is usually made with difficulty. In our study both groups of patients (with and without decreased FT_3 or FT_4) were given comparable quantities of antirheumatic drugs including glucocorticoids. Patients with a history of intravenous pulsed cyclophosphamide therapy showed significantly decreased FT_3 levels compared to other patients ($P = 0.04$). Although this could be due to a decreased T_3 conversion rate, it alerted us to the importance of following up thyroid function in patients receiving cyclophosphamide.

Fibromyalgia and fibromyalgia tender points were detected significantly more often in patients with T_4 hypothyroidism ($P = 0.003$ and 0.01, respectively). Fibromyalgia was found in 12 of 45 (26.7%) patients in our study, a higher rate than has been found in previous studies.[13,14] There was no correlation with neurospychiatric manifestations of SLE, similar to what has been previously suggested.[15] Evidence of fibromyalgia was correlated with primary T_4 hypothyroidism. The correlation of fibromyalgia and hypothyroidism in SLE patients has been previously described.[16]

Jaccoud's arthropathy was reported significantly more often in patients with positive antithyroglobulin assays ($P = 0.01$). Jaccoud's arthropathy was found in a previous study to be associated with fetal loss, thrombosis (both venous and arterial), and the presence of antiphospholipid antibodies.[17] Our study adds antithyroglobulin antibodies to the list as another entity associated with Jaccoud's arthropathy in SLE patients.

Our results have pointed out the significant frequency of thyroid function disorders in SLE. It therefore emphasises the need for routine thyroid function follow-up to allow an eventual cure.

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