Introduction

Antigen stimulation of resting T-cells triggers synthesis and secretion of interleukin-2, as well as the membrane expression of interleukin-2 receptors (1). Normal peripheral blood mononuclear cells and certain lines of T- and B-cell origin, release, after its membrane expression, a soluble form of interleukin-2 receptor (sIL-2R); this appears to be a consequence of cellular activation of various cell types that may play a role in the regulation of the immune response (1,2). Patients with autoimmune diseases, haematologic malignant diseases or overt thyroid disease often show high sIL-2R serum levels (3,4,5), however the course of sIL-2R levels in non-thyroidal disease affecting thyroid function has not been adequately explored. Recent studies have shown that patients with tuberculosis (TB) present with low to normal free and total triiodothyronine levels, which rapidly elevate after anti-tuberculosis therapy (6,7,8). The aim of the present study was to evaluate thyroid function parameters in patients with pulmonary TB before and after initiation of anti-TB therapy.

Materials and methods

Sera from 29 ambulatory patients (19 men, 10 women, mean age±SE: 36±3 years, BMI±26) with sputum-smear positive focal pulmonary TB were assayed for sIL-2Rα (Quantikine hIL-2sR EIA assay, R&D Systems, Oxon, UK, normal limits 676-2132 pg/mL), serum basal thyrotropin (Gammacoat hTSH IRMA, INCSTAR, Stillwater, Minnesota, USA, normal limits 0.40-3.10 µIU/mL), total serum thyroxine and triiodothyronine (Amerlex T4 and T3 RIA, Kodak diagnostics, Amersham, UK, normal values at 5.0-14.0 ng/dL and 0.50-1.90 ng/mL respectively) and free triiodothyronine (Free T3 Clinical Assay, INCSTAR, Stillwater, Minnesota, USA, normal limits 1.50-3.20 pg/mL). The intra- and interassay coefficients of variation of these commercially available assays were less than 6%. Measurements were executed twice for each patient; the first sample was obtained before anti-TB therapy and the second after two weeks of isoniazid (300 mg/day), rifampicin (600 mg/day) and pyrazinamide (300 mg/day) treatment. No other medications were administered during the study period.

The patients' HIV status was assessed, with their consent, using a commercial assay (HIV-1/HIV-2 3rd Generation Plus EIA, Abbott GmbH, Deikenheim, Germany) and none was HIV (+). Subsequent Mycobacterium tuberculosis cultures did not reveal in vitro resistance to first-line anti-TB drugs; all the patients completed a standard nine-month anti-TB regimen and made an uneventful recovery. The patients did not have a history of thyroid and/or autoimmune disease.

Between groups comparison of measured values was made with the Kruskall-Wallis non-parametric ANOVA test while correlations abetween sIL-2Rα and the other thyroid function parameters were done with Spearman’s rank correlation test.

 ORIGINAL ARTICLE

**SOLUBLE INTERLEUKIN 2 RECEPTORS’ LEVELS VERSUS THYROID HORMONES LEVELS IN NONTHYROIDAL DISEASE**

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Summary: Serum soluble interleukin-2 receptor levels, basal thyrotropin, total thyroxine, total triiodothyronine and free triiodothyronine were assayed in 29 - otherwise healthy - patients with pulmonary tuberculosis before initiation of antituberculosis treatment and after two weeks of therapy. Twenty seven out of 29 patients presented low-normal total triiodothyronine levels, showing a statistical elevation after anti-tuberculosis therapy. Total triiodothyronine levels before anti-tuberculosis therapy were inversely correlated with levels of serum soluble interleukin-2 receptors. Further investigation on the relationship between soluble interleukin-2 receptor’s levels and thyroid hormones in non-thyroidal disease can be envisaged.

**Key words:** Receptors; Interleukin-2; Thyroid hormones; Tuberculosis

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Results
One patient was hyperthyroid and presented initially with total serum thyroxine and triiodothyronine above the assays' normal limits (16.1 ng/dL and 2.45 ng/mL respectively, with thyrotropin at 15.2 μU/mL), remaining so after anti-TB treatment began (with serum thyrotropin at 16.0 ng/dL, triiodothyronine at 2.74 ng/mL and serum thyrotropin at 2.20 μU/mL). His free triiodothyronine and s-IL-2R-α remained normal in both samplings. Overall hormone and s-IL-2R-α measurements results are presented in Table 1. Mean thyrotropin-sE remained well within normal limits at the first and at the second sampling. Mean total thyroxine-sE did not show any statistically significant differences between measurements. The observed elevation in total triiodothyronine levels (noted in 27/29 patients), after two weeks of anti-TB treatment, was statistically significant (Kruskal-Wallis p=0.05) Mean sE free triiodothyronine showed an increase after the initiation of anti-TB treatment, however these mean values were within normal limits and differences were not statistically significant. Mean sE s-IL-2R-α levels were higher before treatment compared to mean values after treatment began, but not up to statistical significance and within normal limits. With the exception of the hyperthyroid patient, s-IL-2R-α levels were inversely correlated with total triiodothyronine levels before treatment (Spearman’s rank correlation R=0.62, p=0.017), while no correlation was found at the second sampling, after two weeks of anti-TB therapy (Spearman’s R=0.11, p=0.70).

Serum thyrotropin, total thyroxine and free triiodothyronine were not correlated with s-IL-2R-α neither before nor after the initiation of anti-TB therapy.

Table 1: Overall hormone and soluble interleukin-2 receptor measurements results of the patients (n=29) included in the study

| Parameter | 1st sampling (mean±SE) | 2nd sampling (mean±SE) |
|-----------|-------------------------|------------------------|
| Thyrotropin (in μU/mL) | 10.49±1.82 | 9.04±1.73 |
| Total thyroxine (in ng/dL) | 9.91±3.41 | 9.85±3.41 |
| Free thyroxine (in ng/mL) | 3.39±0.68 | 2.99±0.59 |
| Triiodothyronine (in ng/dL) | 1.73±0.05 | 1.90±0.07 |
| Soluble interleukin-2 receptor (in pg/mL) | 1832.174 | 1805.129 |

* comparison of parameters’ results between samplings significant at the p<0.05 level (Kruskal-Wallis non-parametric ANOVA).

Discussion
This study’s patients initially presented with low to normal serum total triiodothyronine levels, which, following anti-TB treatment, showed a small but statistically significant elevation. This is a finding compatible with the low T-3 syndrome (euthyroid sick syndrome) encountered in non-thyroidal disease (8). A significant negative correlation was observed between serum total triiodothyronine and s-IL-2R-α in patients with TB, a non-thyroidal disease, before administration of anti-TB treatment. Consistently high levels of s-IL-2R-α have been found in patients with untreated Graves’ disease and toxic adenoma (4), while low levels of s-IL-2R-α have been consistently measured in hypothyroid post-thyroidectomy patients (4) and reported in cases of autoimmune thyroiditis (10). Levels of s-IL-2R-α have been shown to be affected essentially in severe cases of TB and in immunocompromised patients (9). The patients of this study were not immunocompromised and made an uneventful recovery, so in this setting, one can also speculate (given the small overall variations), a relation between thyroid hormones and s-IL-2R-α in the low-T3 syndrome. Since the measurement of s-IL-2R-α has already been proposed as an indicator of disease activity in Graves’ disease (11) and an early response marker in thyrotoxicosis’ treatment (5), further relevant studies can be envisaged, in order to assess the behavior and clinical utility of s-IL-2R-α levels versus thyroid function parameters in non-thyroidal disease.

Conclusion
Soluble serum interleukin-2 receptor alpha levels were found to be inversely correlated with total triiodothyronine levels in 29 otherwise healthy patients with pulmonary tuberculosis and the low-T3 syndrome before the administration of antimicrobial therapy. Further studies can be envisaged, in order to assess the behavior and clinical utility of this receptor’s levels versus thyroid function parameters in non-thyroidal disease.

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| Original Article |
|------------------|
| Changes of signal-averaged ECG in normal subjects after one year |
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Summary: Repeated signal-averaged electrocardiograms (SA ECG) were recorded twice with a mean interval of 13 months in 11 healthy volunteers in order to acquire basic information on long-term changes of SA ECG. After one year the duration of filtered QRS remains the most stable parameter of SA ECG on the contrary to parameters describing end of QQRS - i.e. both HFLA and RMS. Moreover iQRS seems to have better specificity in comparison to HFLA and RMS. An estimation of significant long-term changes in individual parameters of SA ECG was obtained. According to our results, only changes in QRS ± 13 ms, iQRS ± 8 ms, HFLA ± 22 ms and RMS ± 17 μs should be considered significant when found in a long-term follow-up of patients with a heart disease.

Key words: Signal-averaged electrocardiography (SA ECG); late potentials; long-term changes; healthy volunteers

INTRODUCTION

Late potentials appear to be a hallmark for sustained ventricular arrhythmias (1). Signal-averaged electrocardiography (SA ECG) helps in stratifying the risk of developing a sustained ventricular arrhythmia in patients who are recovering from myocardial infarction (2). With the present knowledge, it appears that late potentials seem to be more closely related to the underlying morphological substrate for arrhythmias than the clinically occurring arrhythmia per se. Abnormal signal-averaged ECG reflects abnormalities in ventricular activation caused by separation of myocardial bundles and the distortion of their parallel orientation by fibrosis (3).

There are several studies on the long-term changes in SA ECG in patients after myocardial infarction (4,5) and one study of patients with right ventricular dysplasia (6). But assessment of changes of SA ECG was not based on a comparison with a control group. Moreover there has been no study of the long-term changes of SA ECG in normal subjects. In order to acquire such basic information we performed a prospective study of signal-averaged ECG in 11 normal subjects. Such a study should be, in our opinion, the first step in evaluating long-term changes of SA ECG in different group of patients.

MATERIALS AND METHODS

11 men of relatively young age 32±6 years were studied. For inclusion into the study, each subject had to feel healthy and be active. All patients had to have a history and a physical examination neither of which was suggestive of cardiac disease, and a normal surface standard electrocardiogram. Repeated signal-averaged surface electrocardiograms were recorded with a mean interval of 13±1 months.

The recording and signal averaging and processing was performed with a system from Arhythmia Research Technology, model 1200 EPX, based on the method previously described by Simon (1). Standard orthogonal bipolar X, Y, and Z leads were used to manlyse 250 cycles with a noise 0.4 μV. The recorded signals were amplified, averaged and filtered with a Butterworth bidirectional filter (range 40 to 250 Hz). The signal obtained from the 3 leads were then combined to form a vector magnitude (V=√X²+Y²+Z²), a measure that sums the high-frequency content from all three leads, termed ‘the filtered QRS complex’. Three indices were measured: 1. the duration of the filtered QRS (QRS), 2. the root mean square of the terminal 40 ms of the filtered QRS (RMS) and 3. the period for which the filtered QRS remains <40 μV (HFLA). Abnormal values for these three parameters were defined according to current recommendations as QRS >14 ms, RMS <20 μV, and HFLA >38 ms (2). Abnormal late potentials were defined by presence of two criteria out of the three.

All data were expressed as mean ± standard deviation (SD). In order to gain criteria for significant changes for all measured parameters we doubled and rounded up standard deviation of mean change of each of the parameters. Any change in case of QRS, RMS, HFLA higher by 1 ms and in case of RMS higher by 1 μV was considered to be significant (table 1).