

Nebojša Paunkovic*, Džejn Paunkovic*, Kosta Nikolic**

TRAb NEGATIVE ENTITIES OF HYPERTHYROID SYNDROME – OUR EXPERIENCE OF THE PAST 5 YEARS

Abstract: Over the past five years, since we moved to private practice, we continued with testing of TSH receptor antibodies. So far we have carried out 775 tests and examined 260 patients. We used TRAb human, BRAHMs. We carried out our research on 192 patients with untreated immune hyperthyroidism and 37 with the disease in remission. As the subject of this study was TRAb negative hyperthyroidism, the examination of this group of patients was comprehensive. The largest was a group of patients with Plummer disease (13 in total - 4 with toxic adenoma, 7 with multinodular toxic goiter and 2 with disseminated thyroid autonomy). Nine experienced thyroid destruction (eight with painful thyroiditis, one with post-partial thyroiditis and one with thyroid infarction). Five patients had amiodaron induced hyperthyroidism. Diagnosis was based on the following criteria: clinical features and symptoms, 'free' thyroxin concentration, concentration of ultrasensitive TSH, ultrasonography of thyroid gland and scinigraphy with Tc 99m pertehnetat. The analysis of each method was used for diagnosis and differential diagnosis of each type of occurrences of TRAb negative hyperthyroidism.

INTRODUCTION

Hyperthyroidism is basically an increased function of the thyroid gland. It results either from hyperfunction of the entire thyroid gland (diffuse hyperthyroidism) or

* Polyclinic 'Paunkovic' Zajecar, Nuclear Medicine Department at Health Centre in Zajecar. Timočke bune 4, E-mail: npaunkovic@sezampro.rs

** Nuclear Medicine Department at Health Centre in Zajecar, Rasadnička b.b. Zaječar

one part of thyroid gland (focal hyperthyroidism). The aetiology of the disease can be autoimmune, caused by TSH receptor antibodies or autonomous, resulting from autonomous activity of thyroid tissue (toxic adenoma, multifocal thyroid autonomy, disseminated thyroid autonomy). In addition to the above, destruction of thyroid tissue (destructive thyroiditis, painful or painless) can result in raised concentration of thyroid hormone in blood (hyperthyroxinaemia), simulating hyperfunction of thyroid gland. Lastly, the increased uptake of iodine into the human body, mostly by drugs with high iodine concentration (amiodaron) can increase the level of thyroid hormone in blood.

Until recently, only 75% to 90% of all cases of autoimmune hyperthyroidism were TSH receptor antibodies positive, i.e. 10-25% (1,2,3,4,5,6) produced false negative results. Introduction of the second generation of TRAb abolished TRAb negative disease. Basically, all TRAb positive patients have autoimmune hyperthyroidism, Graves – Basedow disease (7,8,9).

The subject of this 5 year- long study was a large group of patients with raised thyroxin in blood and significantly suppressed TSH. We tested patients for TSH receptor antibodies and present the results of the studies.

PATIENTS AND METHODS

Tested Patients

We studied 260 patients, 33 men and 227 women. The youngest patient was 17, the oldest 76 years of age. The test group consisted of 245 patients of various types of occurrence of hyperthyroid syndrome and a control group of 15 euthyroid patients (11 without goiter, 4 with nodular goiter).

The Methods of Testing

All patients were examined by an experienced thyroidologist. The concentration of free thyroxin was measured at least twice. Both FT4 and TSH were tested by fluoroimmunological method (FT4) and fluoroimmunometric method (TSH ultra), using test-kits manufactured by Walac, Finland. We presented earlier (10) characteristics of the test-kits, their normal values and other performance indicators. All patients underwent ultrasound examination (manufactured by Siemens with probe of 7.5 MHz). The majority of patients also had thyroid scintigraphy (camera Open Diacam Siemens, marker Tc 99m pertechnetate). Scintigraphy was carried out in the Department of Nuclear Medicine by an experienced Nuclear Medicine specialist (Dr Kosta Nikolic). TSH receptor antibodies were measured by the luminescent method

of company BRAHMS, now Thermo, chosen on the basis of our long experience (11, 12). All the values above 2 IU/l were considered positive, although in this testing all results were above 3-4.

RESULTS

We presented the results of the study by tables and graphics. In the cases where results are in the forms of pictures (scintigraphy, ultrasonography), we presented few selected examples. Only TRAb negative patients were selected for the case study.

Table 1. Breakdown of patients by diagnosis, total number of tested patients, total number of TRAb tests

Graves disease	Ad toxic	Toxic nodular goiter	transit thyroid	infarct	amiodar	Euthyroid	Total patients	Total tests
181 non treated 31 remiss	4	9	8	1	1	5	11 without goiter 4 with goiter	260 m f 33 227 775

Table 2: Breakdown of patients with TRAb negative hyperthyroidism

Toxic adenoma	Tox nod goiter	Diss thyroid aut	Destruc thyroid	Amiodor	Total
4	7	2	8+1+1	5	28

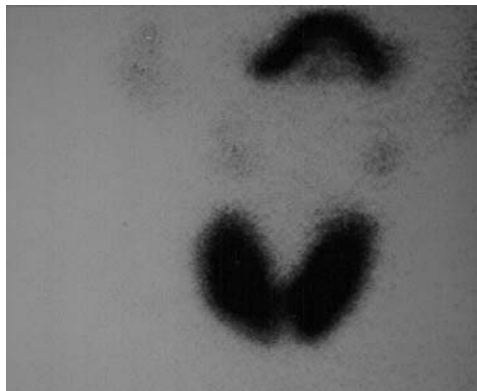


Figure 1. Scintigram, ultrasonogram and laboratories findings in a female patient with Graves disease
UTSH 0.01 mU/l; FT4 78 pmol/l; TRAb 77 IU/l

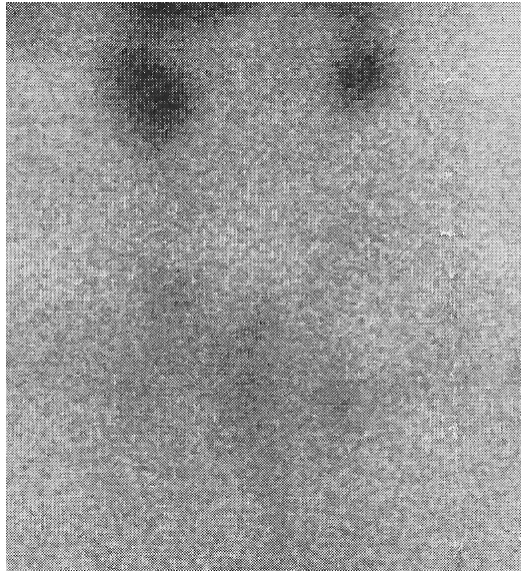


Figure 2 Scintigram and results of hormones and TRAb in a female patient with destructive thyroiditis in a phase of transitory hyperthyroidism

UTSH 0.01 mU/l; FT4 76 pmol/l; TRAb 0.4 IU/ml

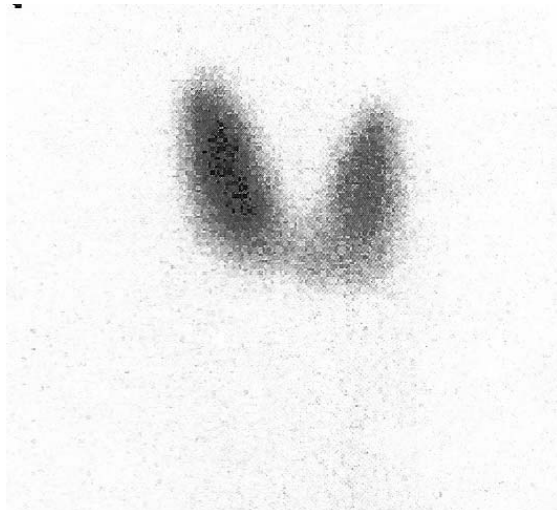


Figure 3. Scintigram of thyroid gland and the results of hormones and TRAb in a patient with disseminated thyroid autonomy

TSH 0.05 mU/l; FT4 16.8 pmol/l; TRAb 0.9 IU/l

DISCUSSION

Over the past 10 years the diagnostic technology in thyroid pathology achieved far more advanced level than the understanding of the subject. Almost every Health Centre can offer today echosonography of thyroid gland and the whole range of in vitro tests: from testing of hormones in blood (total and free) to immunology and tumor markers. Very often these diagnostic tests are requested by doctors with no real education in thyroid endocrinology, surgeons with their 'minimalistic criteria for tests', general practitioners and even patients themselves. The interpretation of these results can be very difficult: whether the results are reliable or normal considering that the range of normal values for all tests is already preset in the software. Very often, the treatment is decided before the diagnosis is established. Generally, raised T4 is taken as hyper function of thyroid gland, which requires drug tiastat for its treatment. Naturally, the proper procedure should be entirely different: patients visit their doctor about the difficulties they experience. Based on symptoms and signs of the disease, the doctor will carry out diagnostic tests or request them to establish the diagnosis and decide on treatment.

In our region with iodine sufficiency or corrected iodine deficiency, the most frequent type of occurrence of hyperthyroid syndrome is Graves'-Basedow's disease, then Plummer's disease with its subgroups: toxic adenoma, toxic nodular goiter with micronodular variety and very rare disseminated thyroid autonomy. All of the above cause hyperactive thyroid gland i.e. belongs to the group of thyrotoxicosis. Destructive thyroiditis (painful or painless) while undergoing through stages of the development, can cause transitory hyperthyroidism. Finally, amiodaron induced hyperthyroidism is no different than hyperthyroidism caused by other destructive factors (viruses, autoantibodies); it only has protracted course.

In this clinical study we showed that, out of 209 patients with active hyperthyroidism tested on TSH receptor antibodies, 28 (13%) had 'TRAb negative hyperthyroidism' i.e. did not have Graves'-Basedow's disease. Out of mentioned 28, 13 have Plummer's disease, 9 transitory hyperthyroidism (8 during the course of painless thyroiditis and one case of post partal thyroiditis), 5 amiodaron induced, one caused by destruction during hemorrhagic infarction. The above mentioned 28 patients were suspected of immune hyperthyroidism during the course of their treatment, but eventually excluded by TRAb testing. In a clear case of toxic adenoma and subacute De Quervain thyroiditis, it was unnecessary to carry out TRAb test. Clinical features of diseases and less costly methods (scintigraphy, SE) were sufficient to establish the diagnosis. This study cannot serve epidemiological purposes either. The fact that we tested 181 patients with active (untreated) Graves' disease and only 13 with autoimmune hyperthyroidism cannot bring conclusions on incidence of these types of hyperthyroidism. We published these data from the thyroid register (for the region of Timocka Krajina) from 1970 to 2005.

LITERATURE

- Becker W., Reiners Ch., Borner W.: Immunologische Kriterien zur Differentialdiagnose von Schilddrüsenerkrankungen, Therapie Woche, (1985), 35:1167-1176.
- Becker W., Borner W.: Therapeutische Konsequenzen aus der Pathogenese der Hyperthyreose, Die Medizinische Welt, (1986), 37:649-653.
- Henning: TRAK-Assay, Prilog uz prospekt, Berlin, 1987.
- Kozak B., Lauterbach W., Ledda R., et al.: Sonographic patterns and TSH-receptor autoantibody titers in immunogenic and non-immunogenic thyrotoxicosis before and after radioiodine therapy, European Nuclear Medicine Congress, London, 1985.
- Orgiazzi J., Madec A.M.: Stimulateurs thyroïdiens autres que la TSH, Ann Endocr (Paris), (1982), 43:509-519.
- Paunković N., Miladinović J., Pavlović O.: Determination of TSH-receptor autoantibodies in different phases of Graves-Basedow disease. European Nuclear Medicine Congress, Goslar, 198
- Morgenthaler NG, Struck J, Weglohner W, Hollidt JM, Bergmann A, Dumon JE. Application of affinity immobilized human recombinant TSH-receptor for the routine measurement of autoantibodies in patients with Graves' disease. ETA '98, Athens, Abstract 138.
- Costagliola S, Morgenthaler NG, Hoermann R, Badenhoop K, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab 1999; 84:90-97.
- Morgenthaler NG. New assay systems for thyrotropin receptor antibodies. Curr Opin Endocrinol 1999; 6:251-260.
- Paunković J., Paunković N. Određjivanje koncentracije TSH senzitivnim i ultrasenzitivnim metodama. Sastanak podružnice SLD, Pirot, 1996. Predavanje po pozivu.
- Paunkovic N, J. Paunkovic. Diagnostic sensitivity of two radioreceptor assays (TRAK-Assay and TRAK dyno human) for detection of TSH-receptor antibodies. Nuclear Medicine Review, 6 (2): 119-122, 2003.
- Paunkovic J., Paunkovic N. Does Autoantibody-negative Graves' disease exist? A second evaluation of the clinical diagnosis. Horm Metab Res 2006,38:48-52.
- Paunkovic J., Aleksic Z., Mitov A., Aleksic A., Paunkovic N. The research of iodine status in East Serbia (Timok region) – thyromobil project. Journees Internationales d'endocrinologie clinique, Paris, 2002, poster 13.
- Paunković N., Paunković Dž. Tranzitorna hipertireoza kao posledica hemoragičnog tireoidnog infarkta u toku tomboembolijske bolest – prikaz bolesnika. Medicinski Glasnik, 14 (30): 7-10, 2009.
- Paunkovic N., Paunkovic J. The follow-up of incidence of autoimmune hyper and hypothyroidism in Eastern Serbia during 24 years, ETA meeting, Edinburgh, 2003. p. 100, abstr P-132.