

MEDICAL CENTRE ZAJECAR, SERVICE OF NUCLEAR MEDICINE

## **VALUES OF TSH RECEPTOR AUTOANTIBODIES IN PATIENTS WITH TREATED GRAVES' DISEASE**

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### **INTRODUCTION**

Thyrotropin receptor autoantibodies (TRAb) are the most frequent thyroid stimulatory immunoglobulins (TSI, TSAb) although they (TSAb) sometimes coexist with thyroid-blocking antibodies (TSBAb) or change into them during hyperthyroidism (1-4). Treatment of Graves' disease (antithyroid drugs, thyroidectomy, radioactive iodine) should influence TRAb circulatory levels (5,6).

Follow-up of TRAb in 114 treated patients and comparison of findings with thyroid hormone levels in clinical states are presented.

### **PATIENTS AND METHODS**

The investigation was conducted in 114 patients with Graves' disease divided into three groups, based on type of treatment. Group I consisted of 66 patients treated with methimazole (Favistan, Bosnalijek). Duration of treatment was 18-21 months. Starting dose was usually 60 mg daily and was diminished during treatment according to metabolic state of patient. Thyroid hormone were not added. Follow-up of patients was performed during the whole treatment and at least six months after that. Group II consisted of 25 patients treated with radioactive iodine ( $^{131}\text{I}$ ). Therapeutic dose was applied once in 16 patients, twice in 8 and three times in 1 patient. In 9 patients of this group, follow-up was performed from the application of radioactive iodine up to 12 to 60 months. In 16 patients check-up was performed only once (last application of radioiodine was more than 5 years ago). Group III consisted of 23 patients with bilateral subtotal thyroidectomy. In 11 patients follow-up began right after surgery and lasted 12 to 36 months, while in 12 patients check-up was done only once (patients operated on more than five years ago).

Thyroid metabolic status of patients was evaluated by two independent experienced endocrinologists. Serum levels of thyroid hormones were determined by routine RIA, and receptor-TSH autoantibodies were determined by radioreceptor assay (TRAK-assay, Henning).

### **RESULTS**

The obtained results are presented in Tables 1,2 and 3. Serum levels of TRAb in follow-up studies are indicated by arrows: with decreasing magnitude to normalization, or continuously elevated in patients with permanent high TRAb. Results are illustrated in four cases (2 treated with metimazole and 2 surgically) (graphs 1-4).

Table 1 – Graves' disease, 66 patients, methimazole follow – up during treatment (18–21 months) and at least 6 months after cesation

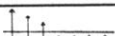
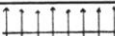
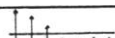
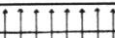
TRAb				total
n	47	19		66
issue	eu	hiper	hypo trans	total
	47	12	7	66
relapse	7	12	3	22

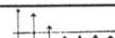
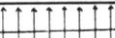
Table 2 – Graves' disease, 25 patients, <sup>131</sup>I therapy follow – up (12 – 60 months)

TRAb				total
n	5	4		9
issue	eu	hypo	hyper (12 months)	total
	4	1	4	9

Testing in remission (over 5 years)

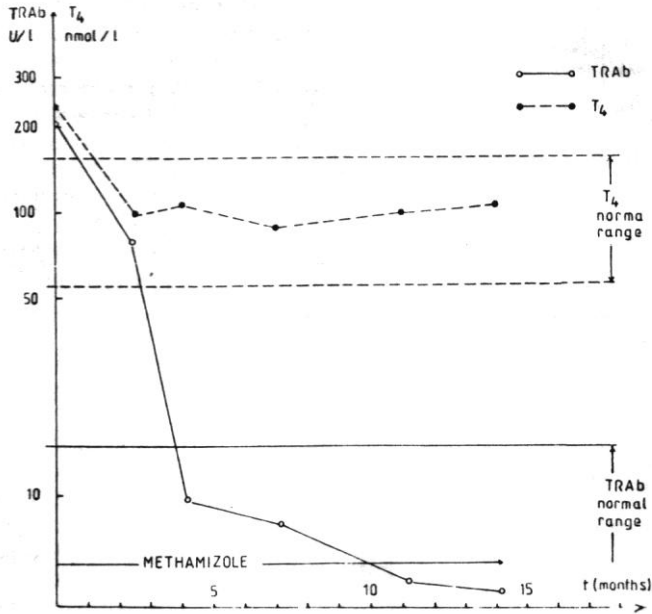
TRAb	normal	high		total
n	15	1		16
issue	eu	hypo	hypo	total
	13	2	1	16

Table 3 – Graves' disease, 23 operated patients follow – up (12 – 36 months)

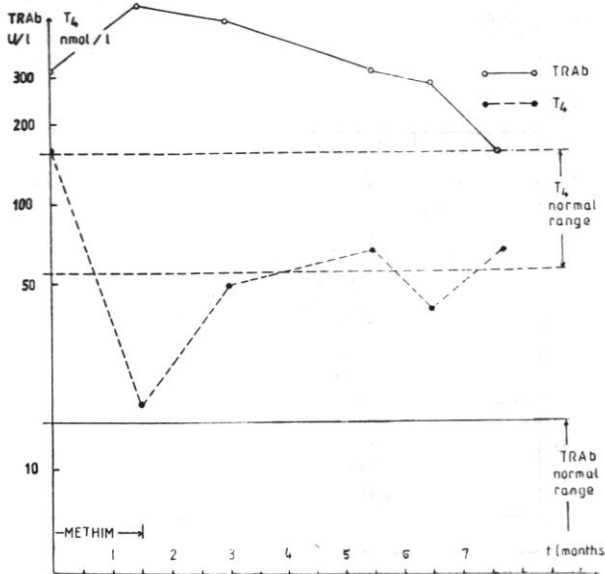
TRAb				total
n	5	6		11
issue	eu	hypo	eu	total
	4	1	5	11
			hyper	
			1	

Testing in remission (over 5 years)

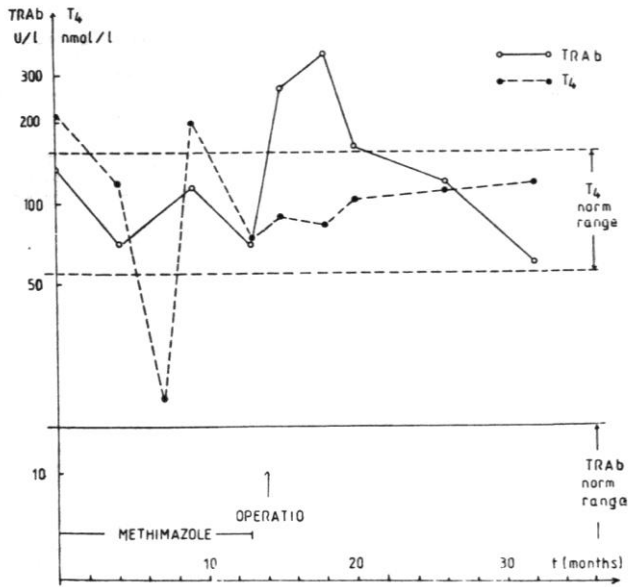
TRAb	normal	high		total
n	11	1		12
issue	eu	hypo	eu	total
	8	3	1	12



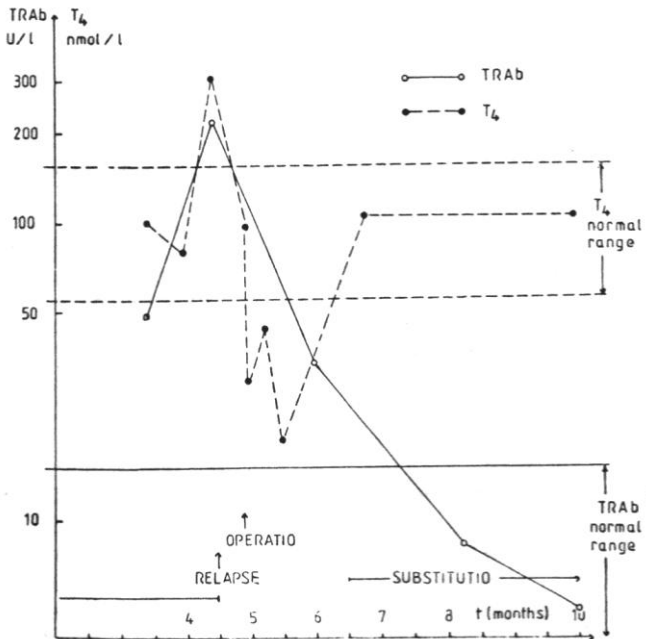
Graph 1 – Case report: concordant normalization of T<sub>4</sub> and TRAb under methimazole treatment



Graph 2 – Case report: persistence of high TRAb levels and low T<sub>4</sub> after a short methimazole therapy (TBAb?)



Graph 3 – Case report: persistence of TRAb few months after subtotal thyroidectomy with euthyroidism



Graph 4 – Case report: early postoperative hypothyroidism and rapid TRAb decrease

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## DISCUSSION

Of 66 patients treated with methimazole more than 70% (47 patients) were good responders (reestablishment of remission, TRAb normalization). These findings are slightly better than some recently reported data (7). There is an attractive hypothesis that methimazole has an immunosuppressive effect which results in diminished TRAb serum levels and consequent normalization of thyroid metabolic and hormonal state (4,8). It should also be considered that TRAb normalization could be a consequence of decrease in thyroid hormones levels as a result of direct thyrostatic action of methimazole (9). In 12 patients in spite of high doses of methimazole hyperthyroidism was persistent with elevated TRAb levels (nonresponders). In 7 patients despite high TRAb concentrations, transitory hypothyroidism was observed. We have not tested TRAb activity by postreceptor effects (cAMP generation), but we assume that the high TRAb concentrations accompanying hypothyroidism point out their thyroblocking effects (4,10).

Patients with persistently elevated TRAb levels, several months after  $^{131}\text{I}$  therapy, remained hyperthyroid (all of them required additional therapeutic dose). Patients in longer remission after radioiodine therapy had normal TRAb levels. These findings are not in accordance with some reports in which patients in remission exhibit high TRAb levels (11) but are similar to others (12). Low incidence of hypothyroidism in our group of treated patients is probably due to application of low doses of  $^{131}\text{I}$  (3 MBq/g). These low doses have effect on the lymphocytes of the thyroid responsible for TRAb production, and have not enormous thyronectrotic effect (13).

After bilateral subtotal thyroidectomy, functional status is normalized prior to TRAb levels (in 6 of 11 in early follow-up study). In one patient with early postoperative hypothyroidism rapid TRAb decrease was registered. Patients in longer remission had normal TRAb levels.

Our results support opinions that TRAb (TSAb) have important role in pathogenesis of immunogenic hyperthyroidism. However, some observations must be supplemented by following investigations ( distinguishing thyrostimulating from thyroblocking antibodies) or by testing some immunologic factors other than TRAb (thyroid microsomal antibodies ets).

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