ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 1, 46 SECTIO D 2003

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Changes in TSH receptor antibody levels (TRAb) as markers of effectiveness of various therapies in Graves-Basedow`s disease

Graves-Basedow`s disease is an illness in the pathogenesis of which the main role is played by the TSH receptor antibodies (TRAb). Their serum concentration is one of the factors indicating the severity of immune defects.

The aim of the study is to evaluate the usefulness of TRAb determinations in predicting and monitoring the effectiveness of treatment of Graves-Basedow`s disease depending on the type of therapy used.

MATERIAL AND METHODS

The study included 144 patients with Graves-Basedow`s disease, 108 women and 36 men whose age ranged from 18 to 76 years, $\bar{x}$– 44. The results were analysed in the individual groups according to the type of treatment. Group I (n=54) – the patients treated with thiamazole, Group II (n=45) – the patients treated with ^{131}I, Group III (n=45) – the patients subjected to subtotal strumectomy. The control group (n=20) consisted of healthy volunteers without any clinical or biological features of thyroid diseases. This group included 15 women and 5 men aged 22-45, $\bar{x}$– 34.

The levels of TSH receptor antibodies were analysed before and 12 months after treatment (the group subjected to surgery) and before, 12 and 18 months after treatment (the groups treated with thiamazole and ^{131}I). Additionally, the levels of TSH and FT4 were determined. The TSH receptor antibodies were determined using the radioimmunoassay (TRAK-assay, Henning). The reference range was 0–9 U/l.

Statistical analysis. The examined parameters were expressed as the arithmetic mean and standard deviation. The statistical analysis was performed by means of Student's t and Wilcoxon tests. The level of statistical significance was calculated using the Statistica program. The differences were considered statistically significant at $p<0.05$.

RESULTS

The evaluation of clinical condition and determinations of TSH and FT4 levels showed:

In the group treated with thiamazole (18 months after treatment): in 31 patients (57%) the thyroid function normalized (euthyreosis), in 23 patients (43%) the therapy was ineffective (hyperthyreosis)

In the group treated with ^{131}I (18 months after therapy): in 12 patients (27%) the thyroid function normalized (euthyreosis), in 15 patients (33%) hypothyroidism was observed (hypothyreosis), in 18 patients (40%) the therapy was ineffective (hyperthyreosis)

In the group subjected to surgical treatment (12 months after surgery): in 19 patients (42%) the thyroid function was normal (euthyreosis), in 13 patients (29%) the symptoms of hypothyroidism developed (hypothyreosis), in 13 patients (29%) recurrence of hyperthyroidism was found (hyperthyreosis).

The table below presents the mean values and statistically significant differences in the TSH receptor antibody levels in the individual clinical groups according to the therapy and its effects. The highest initial TRAb values, irrespective of the type of treatment, were found in the groups in which the therapy was ineffective (the thiamazole group $\bar{x}$-54.39± 31.23 U/l, the radioiodine group $\bar{x}$-103.61± 43.90 U/l and in the surgery group $\bar{x}$-104.00± 52.34 U/l). During the 12-month-follow up, despite a slight decrease in TRAb values, normalization was not achieved ($\bar{x}$-39.96 ± 33.40U/l, $\bar{x}$-63.33 ± 29.77U/l, $\bar{x}$-58.77 ± 54.67 U/l, respectively).

Table 1. Variations in TRAb levels in the individual clinical groups

TRAb	Thiamazole		^{131}I			Surgical procedure		
	EUT n=31	HPR n=23	EUT n=12	HYP n=15	HPR n=18	EUT n=19	HYP n=13	HPR n=13
Before treatment	x- 29.13 ± 19.14 A, *A*	x-54.39 .± 31.23 a, b, *A*	x- 36.67 .± 15.45 B, *A*	x-62.33 ± 46.35 B, *A*	x-103.61 ± 43.90 *A*	x-23.84 ± 11.55 C, *A*	x-24.38 ± 9.71 C, *A*	x-104.00 ± 52.34 *A*
After 12 months	x-9.87 ± 8.33 A	x- 39.96 ± 33.40 b, c, *A*	x-9.58 ± 5.82 B	x-7.67 ± 3.45 B	x-63.33 ± 29.77 *A*	x-6.53 ± 6.23 C, *B*	x-2.08 ± 1.44 C	x-58.77 ± 54.67 *A*
After 18 months	x- 4.45 ± 2.94 A	x-40.17 ± 33.06 c, *A*	x-6.08 ± 3.73 B	x-7.07 ± 5.17 B	x-77.18 ± 44.92 *A*			
Controls x-2.75±2.06 U/l								

EUT – euthyreosis, HYP – hypothyreosis, HPR – hyperthyreosis
a – p<0.01 compared to the group treated with ^{131}I with persistent hyperthyroidism
b – p<0.01 compared to the group subjected to surgery with recurrent hyperthyroidism
c – p<0.05 compared to the group treated with ^{131}I with persistent hyperthyroidism

A – p<0.001 compared to the group treated with thiamazole with persistent hyperthyroidism
B – p<0.001 compared with the group treated with ^{131}I with persistent hyperthyroidism
C – p<0.001 compared with the group subjected to surgery with recurrent hyperthyroidism

A – p<0.001 compared to controls
B – p<0.01 compared to controls

Moreover, the decreased TSH levels were still observed in the groups treated conservatively and recurrent hyperthyroidism was found in the patients subjected to surgery. At 18 months of follow-up the antibody levels were still increased in the thiamazole and ^{131}I groups in the patients in whom the treatment was ineffective. In the groups subjected to conservative treatment without effects statistically significantly decreased TRAb values were observed after 12 months and normalization after 18 months. In the patients subjected to surgery, TRAb normalization was found 12 months after the procedure.

DISCUSSION

Increased antibody levels in Graves-Basedow's disease are recognized sensitive markers of the illness [6]. A different issue concerns the usefulness of antibody determinations in predicting the effectiveness of thyreotoxicosis treatment.

Michelangeli (8) evaluates that TRAb variations in the first 6 months of conservative treatment with thyreostatics do not make it possible to select the patients in whom remission is expected. The author states that if the antibody normalization is achieved at 12 month of treatment, the recovery chances are 70%. Similar results are presented by Allannic et al. (2), who evaluated the patients subjected to short-term (6 months) and long-term therapy (18 months). The changes in TRAb levels in the group treated for 6 months do not provide explicit evaluation of the therapy effectiveness. The studies by Wilson (14) revealed that when hyperthyroidism was still observed after a year of thyreostatics treatment, increased levels of TRAb were found in 83% of the patients. When normalization was achieved, the hyperthyroidism symptoms were observed in 5% of the patients. Our studies show that during the 12 months' treatment with thyreostatics the changes in TRAb levels may allow to select the patients in whom this form of treatment should be continued and those who might require radical treatment. Moreover, the majority of authors believe that the initial TRAb level before treatment is an important prognostic marker of the conservative therapy effectiveness (3,4). High values of TSH receptor antibodies suggest high stimulation of the immune system resulting from the severe defect within the system and worsen the prognosis of achieving euthyreosis. Our findings confirm worse prognosis concerning recovery in the group with higher initial antibody values.

The levels of TRAb after ^{131}I therapy have already been described in literature. Aizawa et al. (1)] evaluated the group of more than 200 patients treated with ^{131}I. The initial TRAb levels were increased in 78% of the patients. After 3 months an average increase in TRAb levels was observed in about 10% of the patients compared to the initial values. Increased antibody levels were found in 85% of the patients. After a year, increased antibody levels were still observed in 63%, after 18 months – in 49%. Furthermore, over 2-year follow-up showed that 42% of the patients with increased TRAb levels developed recurrent hyperthyroidism, while only 8% of those with normalized antibody levels. The studies performed by Yoshida et al. (14)] demonstrated that evaluating the hormonal condition 6–14 years after ^{131}I therapy, increased antibody levels were observed in 48% of the patients with recurrent hyperthyroidism and in 5% of those with hypothyroidism. Our studies of all the patients treated with ^{131}I showed increased TRAb values before the therapy. The highest antibody values before the administration of iodine were observed in the patients with persistent hyperthyroidism. In this group no normalization was achieved within the 18-month follow-up.

Nowadays the surgical treatment for Graves-Basedow's disease is the most infrequent method used. Examining the level of antibodies before and after the surgical procedure, the Japanese authors (11) found that it was not a proper marker of the operation effectiveness. If the postoperative TRAb values markedly diminished or normalized, and particularly if they show an increasing tendency, there is a high risk of hyperthyroidism recurrence. Increased levels of TRAb before operation, despite euthyreosis as a condition deciding about undertaking the

surgical procedure, are also of poor prognostic value. They indicate the immune system stimulation despite previous suppression with thyreostatics (7,10).

Sugino et al. (12) evaluated early hyperthyroidism recurrences after surgery. The authors define early recurrence as the development of hyperthyroidism within the year following the operation and its maintenance for at least 6 months. Such recurrences were observed in about 15% of the operated patients. The authors found a positive correlation between the hormonal condition of the thyroid gland and TRAb levels. A similar correlation was also noted by Rubello et al. (9) and Domoslawski et al. (5). Our studies showed that TRAb levels were increased before surgery in all the patients. In the patients with recurrent hyperthyroidism observed after 12 months, TRAb normalization was not achieved. Our findings confirmed that high initial TSH receptor antibody values deteriorated the prognosis. Among the patients with recurrent hyperthyreosis, the initial TRAb levels were almost 4 times higher than those in the patients with postoperative euthyreosis or hypothyreosis.

The results presented above prove the usefulness of TSH receptor antibody determinations in predicting the effectiveness and monitoring the treatment in Graves-Basedow's disease, irrespective of the type of therapy instituted. In the conservative treatment, lower initial TRAb levels and their normalization 12 months after the onset of treatment may be treated as one of the factors suggesting the continuation of therapy. The TRAb values may also be used to predict the effectiveness of ^{131}I therapy. High initial antibody levels may suggest a need for increased doses, determination of antibodies after treatment allow us to select the group with high risk of persistent or recurrent hyperthyroidism. In the surgical treatment, high initial TRAb values justify more extensive procedure, and after operation may enable the endocrinologists to choose the group of patients with high risk of reccurrence.

CONCLUSIONS

1. The level of TSH receptor antibodies is a good marker for predicting the treatment effectiveness in Graves-Basedow's disease.
2. A high initial antibody level, irrespective of the therapy form, is an unfavorable prognostic factor.
3. Beside the pretreatment antibody levels, the TRAb determinations performed after 12 months are of good prognostic value.
4. The lack of normalization of antibody levels during treatment is associated with persistent hyperthyroidism, irrespective of the type of treatment.

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SUMMARY

The aim of the study was to evaluate the usefulness of TRAb determinations in predicting and monitoring the effectiveness of various forms of treatment in Graves-Basedow's disease. 144 patients with Graves-Basedow's disease aged 18–76 years, $\bar{x}$ – 44 were studied. Group I–54 patients treated with methizole, group II–45 patients treated with ^{131} I, group III–45 patients subjected to operative procedures. The TSH receptor antibodies were determined using the radioimmunoassay (TRAK-assay, Henning). The examinations were performed before, 12 and 18 months after treatment. Irrespective of the treatment type, the highest initial TRAb values were observed in the groups of patients with ineffective treatment (thiamazole $\bar{x}$ – 54.39± 31.23 U/l, radioiodine $\bar{x}$ – 103.61± 43.90 U/l, operative procedures $\bar{x}$ – 104.00± 52.34 U/l). During the 12–month follow–up of the patients subjected to surgery and 18-month follow-up of those undergoing conservative treatment, the level of antibodies did not normalize ($\bar{x}$ – 40.17± 33.06, $\bar{x}$ – 77.18± 44.92, $\bar{x}$ – 58.77± 54.67, respectively). In the groups with effective treatment, the TRAb levels normalized. 1. The level of TSH receptor antibodies is a good marker for monitoring the effectiveness of treatment in Graves-Basedow's disease. 2. The high initial antibody level, irrespective of the kind of treatment instituted, is a bad prognostic feature. 3. The TRAb determinations performed 12 months after the institution of treatment also show some prognostic value. 4. The lack of normalization of antibody levels during treatment is associated with persistent hyperthyroidism, irrespective of the form of therapy.

Zmiany poziomu przeciwciał przeciw receptorom TSH (TRAb) jako wskaźnik skuteczności leczenia choroby Graves-Basedowa w zależności od rodzaju podjętej terapii

Celem pracy jest ocena przydatności oznaczeń TRAb w prognozowaniu i monitorowaniu skuteczności leczenia choroby Graves-Basedowa w zależności od rodzaju podjętej terapii. Materiał kliniczny i metoda: 144 osoby z chorobą Graves-Basedowa, w wieku od 18 do 76 lat, $\bar{x}$ – 44 lata. Grupa I – 54 chorych leczonych Tiamazolem, grupa II – 45 chorych leczonych ^{131}I, grupa III – 45 chorych leczonych operacyjnie. Przeciwciała przeciw receptorom TSH oznaczano metodą radioimmunologiczną przy użyciu zestawu TRAK-assay firmy Henning. Oznaczenia wykonano przed leczeniem, po 12 i 18 miesiącach. Niezależnie od formy leczenia najwyższe wyjściowe wartości TRAb zanotowano w grupach chorych, u których leczenie było nieskuteczne (leczeni Tiamazolem $\bar{x}$ – 54,39 ± 31,23 U/l, radiojodem $\bar{x}$ – 103,61 ± 43,90 U/l, operowani $\bar{x}$ – 104,00 ± 52,34 U/l). W dalszej 12-miesięcznej obserwacji chorych operowanych i 18-miesięcznej chorych leczonych zachowawczo nie obserwowano w tych grupach normalizacji poziomu przeciwciał (leczeni Tiamazolem $\bar{x}$ – 40,17 ± 33,06, radiojodem $\bar{x}$ – 77,18 ± 44,92, operowani $\bar{x}$ –58,77 ± 54,67 U/l). W grupach chorych, których leczenie było skuteczne, stwierdzono normalizację poziomu TRAb. Wnioski: 1. Poziom przeciwciał receptorom TSH stanowi dobry wskaźnik, pozwalający na monitorowanie skuteczności leczenia choroby Graves-Basedowa. 2. Wysoki wyjściowy poziom przeciwciał, niezależnie od podjętej formy leczenia, jest niekorzystnym czynnikiem prognostycznym obciążającym rokowanie. 3. Wartość prognostyczną, poza oceną poziomu przeciwciał przed leczeniem, mają oznaczenia TRAb wykonane 12 miesięcy po wdrożeniu terapii. 4. Brak normalizacji poziomu przeciwciał w trakcie leczenia wiąże się z utrzymywaniem nadczynności, niezależnie od formy leczenia.