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CLINICAL SIGNIFICANCE OF ANTIBODIES TO THYROTROPIC HORMONE RECEPTOR AS A BIOMARKER OF GRAVES DISEASE ACTIVITY

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Objective: to study the clinical significance of antibodies to thyroid-stimulating hormone receptors as a biomarker of Graves' disease activity in patients in the Voronezh region. A retrospective study of 76 patients with Graves' disease treated at Voronezh Regional Clinical Hospital #1 from 2018 to 2021 was carried out. Qualitative and quantitative indicators were assessed: anamnestic data, features of the clinical picture, the results of laboratory and instrumental research methods at the first visit, in 6 and 12 months after antithyroid therapy. During the study, 3 groups were formed: group 1 – patients with Graves' disease – 35 people, group 2 – patients with Graves' disease in combination with previously untreated endocrine ophthalmopathy – 41 people, group 3 – control group of 15 people without thyroid disease. Our study found that male gender, smoking, free triiodothyronine levels, the severity of thyrotoxicosis and the presence of endocrine ophthalmopathy had a positive correlation with high levels of antibodies to thyroid-stimulating hormone receptors. Measurement of the level of antibodies to thyroid-stimulating hormone receptors in the blood in patients with Graves' disease helps to assess the course of Graves' disease complicated by endocrine ophthalmopathy and allows to determine the risk of activity and severity of endocrine ophthalmopathy. Determining the level of antibodies to thyroid-stimulating hormone receptors is recommended not only for rapid diagnosis, differential diagnosis, but also for monitoring the adequacy of treatment of patients with Graves' disease.

Keywords: Graves' disease, antibodies to the thyroid-stimulating hormone receptor

Pathological and physiological mechanisms of the formation of Graves' disease are under the influence of stimulating antibodies to the thyroid-stimulating hormone receptor due to hypersecretion of thyroid hormones, which develops diffuse thyroid damage, thyrotoxicosis syndrome, and extrathyroid pathology [1, 2]. Endocrine ophthalmopathy is the most common non-thyroidal manifestation of Graves' disease with an incidence of 42.2/million people per year [3].

About 80% of all cases of hyperthyroidism are due to Graves' disease [4]. The prevalence of thyrotoxicosis in Russia in 2001 was 18.4 cases per 100,000 people [1]. In the Voronezh region in 2018, 17.6 cases were detected per 100,000 people, while in a number of territories the incidence rate significantly exceeded this indicator [5].

The autoimmune nature of Graves' disease has formed a vector for the search for the most informative immunological markers of the disease, among which today one of the leading places belongs to the antibodies to thyroid-stimulating hormone receptors. Antibodies to thyroid-stimulating hormone receptors are specific biomarkers of Graves' disease and associated endocrine ophthalmopathy, which affect the pathogenesis and course of the disease [6].

In respect that Graves' disease and endocrine ophthalmopathy most often develop in people of working age [1], the study of the clinical utility and prognostic value of antibodies to thyroid-stimulating hormone receptors is relevant and can help determine the choice of treatment tactics for this pathology.

Objective: to study the clinical significance of antibodies to thyroid-stimulating hormone receptors as a biomarker of Graves' disease activity in patients in the Voronezh region.

Materials and methods of research

A retrospective study of 76 patients with Graves' disease treated at Voronezh Regional Clinical Hospital #1 from 2018 to 2021 was carried out. Among these there were 57 women and 19 men, aged 28 to 67 years, the average age was 43.4±12.8 years.

The study did not include patients with nodular neoplasms resulting from Graves' disease, patients with relapse of Graves' disease who had previously been operated on or received radioiodine therapy, as well as patients with Graves' disease with inactive endocrine ophthalmopathy.

When making a diagnosis, first of all, blood counts for thyroid-stimulating hormone, the level of free thyroxine, free triiodothyronine, and antibodies to the thyroid-stimulating hormone receptor were taken into account.

Manifest thyrotoxicosis was diagnosed in 64 patients (84.2%), complicated thyrotoxicosis was diagnosed in 12 patients (15.8%) with atrial fibrillation.

The titer of antibodies to the thyroid-stimulating hormone receptor ranged from 3.8 to 40 IU/l (reference values: ≤ 1.75 IU/l – negative, >1.75 IU/l – positive), averaged 25.6±11, 4 IU/l.

All patients underwent an ultrasound examination of the thyroid gland with color Doppler flow mapping, which found that against the background of a diffuse decrease in echo-

genicity, an increase in the level of blood supply to the tissue of both lobes of the thyroid gland was clearly seen, in accordance with the international classification – TIRADS II. The volume of the thyroid gland ranged from 15.6 cm3 to 68.5 cm3, averaging 41.7±18.4.

Scintigraphy was performed in 14 patients (18.4%) for the purpose of differential diagnosis, computed tomography – in 1 patient (1.3%) with a low thyroid gland and suspected retrosternal goiter.

Patients with endocrine ophthalmopathy were examined and consulted by an ophthalmologist. When diagnosing endocrine ophthalmopathy, activity and severity were determined for the most affected eye, taking into account EUGOGO recommendations [7]. Clinical activity was diagnosed using the CAS clinical activity scale, and the severity was set according to the NOSPECS classification [8]. In all patients, endocrine ophthalmopathy was detected for the first time during examination for Graves' disease and was in an active form according to CAS from 3 to 7 points.

Qualitative and quantitative indicators were assessed: anamnestic data, features of the clinical picture, the results of laboratory and instrumental research methods at the first visit, in 6 and 12 months after conservative treatment – antithyroid therapy.

All patients received monotherapy or "block and replace" treatment for 12 months. Blood control for thyroid stimulating hormone, thyroxine and triiodothyronine was done throughout the treatment; the titer of antibodies to thyroid-stimulating hormone receptors was determined after 6 months, as well as during the normalization of thyroid status before the abolition of antithyroid drugs 12 months after treatment.

Statistical analysis was carried out using the statistical data analysis software package Statistica, 9.1 and Microsoft Excel for Windows.

Descriptive statistics of qualitative features are given by absolute or relative frequencies. When analyzing quantitative traits, the following were determined: mean, minimum, maximum values, standard deviations (M ± SD, where M is the arithmetic mean).

Differences between groups with a normal distribution of a trait were assessed using Student's t-test, in groups that differ from the normal distribution of a trait the Mann-Whitney test with a critical significance level of 0.05 ($p < 0.05$) was taken. When analyzing the nature and strength of the relationships between the indicators, the Spearman correlation coefficient was determined.

Results of the research and discussions

During the study, 3 groups were formed. Two clinical groups: the first group – patients with Graves' disease – 35 people and the second group – patients with Graves' disease in combination with previously untreated endocrine ophthalmopathy – 41 people.

The indicators of the two clinical groups were compared with the results of the examination of the control group (group 3) – 15 people without thyroid disease, similar in sex and age, who considered themselves practically healthy and were examined by various doctors during medical examination.

We have analyzed the main clinical data of the primary examination of patients in the study groups. All patients were divided according to gender, age, smoking habit, thyroid volume, thyrotoxicosis severity, endocrine ophthalmopathy activity (CAS – clinical activity score), endocrine ophthalmopathy severity (NOSPECS), and thyroid-stimulating hormone receptor antibody levels.

The assessment of correlations between the titer of antibodies to thyroid-stimulating hormone receptors and clinical signs of Graves' disease and endocrine ophthalmopathy at the initial stage of eye disease was performed.

The study included 57 women (75%) and 19 men (25%). In the first group 29 women (82.9%) and 6 men (17.1%), in the second group 28 women (68.3%) and 13 men (31.7%). The proportion of men is statistically significantly higher than women ($p=0.02$) in patients with Graves' disease in combination with endocrine ophthalmopathy.

The levels of antibodies to thyroid-stimulating hormone receptors were significantly higher in men compared to female patients in both the first and second groups, $p = 0.049$ and $p = 0.038$ respectively, which is confirmed in the works of other authors [9, 10].

The age of patients ranged from 28 to 67 years, the average age was 43.4±12.8 years, while in patients with Graves' disease without endocrine ophthalmopathy – 39.1±11.4 years, in patients with endocrine ophthalmopathy – 42.2 ±12.3 years, in the control group – 40.7±9.1 years. There was no statistically significant difference in age in all three groups ($p > 0.05$).

27 people (35.5%) had a smoking habit, in which 8 patients (22.9%) in the first group, 19 (46.3%) in the second group, there were no smokers in the control group. Among patients with Graves' disease in combination with endocrine ophthalmopathy, there are statistical-

ly significantly more smokers than non-smokers (p=0.017).

Thyroid-stimulating hormone receptor antibody levels were significantly higher in smokers in comparison with non-smokers in both groups (p=0.047, p=0.0031), which corresponds to the data of other authors [9].

The volume of the thyroid gland ranged from 15.6 cm3 to 68.5 cm3, averaged 41.7±18.4, in the first group – 32.3±11.4 cm3, in the second group – 46.8±14.7 cm3, in the control group – 18.7±6.2 cm3. When comparing the results of the study groups, it was found that a statistically significant increase in the thyroid gland was observed in the group of patients with Graves' disease in combination with endocrine ophthalmopathy in comparison with the group of patients with Graves' disease without endocrine ophthalmopathy and the control group (p1.2=0.049, p2.3= 0.018), as well as in the group of patients with Graves' disease without endocrine ophthalmopathy in comparison with the control group (p1.3=0.031).

The study of correlations between the level of antibodies to thyroid-stimulating hormone receptors and indicators of thyroid status in patients with Graves' disease showed that antibody titers to thyroid-stimulating hormone receptors positively correlated with the level of free triiodothyronine in the blood (p = 0.025) and negatively with the level of thyroxine (p = 0.034) .

Manifest thyrotoxicosis was found in 64 patients (84.2%), complicated – in 12 patients (15.8%) with atrial fibrillation. In 12 patients with complicated course of thyrotoxicosis in the first group there were 5 patients with Graves' disease without endocrine ophthalmopathy, in the second group – 7 patients with Graves' disease with endocrine ophthalmopathy. In patients with a complicated form of thyrotoxicosis, the titers of antibodies to thyroid-stimulating hormone receptors were higher than in patients with overt thyrotoxicosis (p = 0.01).

The titer of antibodies to the thyroid-stimulating hormone receptor ranged from 3.8 to 40 IU/l, averaging 25.6±11.4 IU/l. The level of antibodies to thyroid-stimulating hormone receptors in patients of the second group with Graves' disease in combination with endocrine ophthalmopathy is statistically significantly higher than in patients with Graves' disease without endocrine ophthalmopathy 27.7 IU/l versus 14.9 IU/l (p < 0.01), which is consistent with the results of other authors [6].

At the time of the initial visit, the average CAS inflammation activity score was 4 ± 0.2, while low CAS activity from 3 to 4 points was found in 30 patients (73.2%), high CAS activity from 5 to 7 points was found in 11 patients (26.8%. In patients with Graves' disease with high activity of endocrine ophthalmopathy, the titer of antibodies to thyroid-stimulating hormone receptors is statistically significantly higher than in patients with low activity of endocrine ophthalmopathy 31.7 IU/l versus 18.6 IU/l (p<0.001).

The titer of antibodies to thyroid-stimulating hormone receptors positively correlated with the degree of activity of endocrine ophthalmopathy (r = 0.41). Our results do not contradict the studies of domestic and foreign scientists [6, 10, 11, 12].

When examined by an ophthalmologist the severity of endocrine ophthalmopathy was revealed along with the determination of the activity of endocrine ophthalmopathy. A mild degree of endocrine ophthalmopathy (1-2) was diagnosed in 12 patients (29.3%), moderately severe endocrine ophthalmopathy (3-4) – in 29 (70.7%), there were no patients with severe endocrine ophthalmopathy (5-6). In moderately severe endocrine ophthalmopathy, a statistically significant predominance of men was observed (p < 0.05).

The level of antibodies to thyroid-stimulating hormone receptors is statistically significantly higher in moderately severe endocrine ophthalmopathy 21.6 IU/l in comparison with mild endocrine ophthalmopathy 12.9 IU/l (p=0.001), which corresponds to the results of most researchers [6, 10, 12, 13, 14].

Analysis of the results of examination of patients with Graves' disease without endocrine ophthalmopathy and in combination with endocrine ophthalmopathy during the year of treatment with thyreostatics showed that the titer of antibodies to thyroid-stimulating hormone receptors decreased in both groups during 12 months of treatment in 56 of 76 patients (73.7%).

In 11 patients (14.5%), a decrease in titer was first detected within 6 months, and then, from 6 to 12 months, the titer of antibodies to thyroid-stimulating hormone receptors decreased slightly. In 9 patients (11.8%), the titer of antibodies to thyroid-stimulating hormone receptors remained consistently high.

12 months after continuous treatment, antibodies to thyroid-stimulating hormone receptors were detected in 27.6% of patients, their average content did not reach normal levels.

Thus, when the thyroid status is normalized one year after continuous treatment with thyreostatics in patients with Graves' disease, both in combination with endocrine

ophthalmopathy and without it, antibodies to thyroid-stimulating hormone receptors are detected, clinical remission is ahead of the achievement of correction of immunological parameters. At the same time, the activity of endocrine ophthalmopathy decreased in most patients (88.2%) in the first six months, and the severity of endocrine ophthalmopathy remained practically unchanged for 12 months.

Conclusions

In our study, it was found that male gender, smoking, free triiodothyronine level, the severity of thyrotoxicosis, the presence of endocrine ophthalmopathy had a positive correlation with high levels of antibodies to thyroid-stimulating hormone receptors.

Measurement of the level of antibodies to thyroid-stimulating hormone receptors in the blood in patients with Graves' disease helps to assess the course of Graves' disease complicated by endocrine ophthalmopathy, and allows to determine the risk of activity and severity of endocrine ophthalmopathy.

Determination of the level of antibodies to thyroid-stimulating hormone receptors is recommended not only for rapid diagnosis, differential diagnosis, but also for monitoring the adequacy of treatment of patients with Graves' disease, since a slight decrease or no decrease in the titer of antibodies to thyroid-stimulating hormone receptors during treatment or at the end of treatment with thyreostatics is a marker of ongoing autoimmune disease activity.

References

1. Clinical guidelines for the diagnosis and treatment of thyrotoxicosis with diffuse goiter (Graves' disease), nodular / multinodular goiter. 2021. 50 p. URL: https://congress-med.ru/assets/files/2021/2021-rossijskie-rekomendaczii-po-tireotoksikozu.pdf (date of access: 07.11.2022).

2. Bartalena L., Piantanida E., Gallo D., Ippolito S., Tanda M.L. Management of Graves' hyperthyroidism: present and future. Expert Rev Endocrinol Metab. 2022. № 17(2). P. 153-166. DOI: 10.1080/17446651.2022.2052044.

3. Nowak M., Marek B., Kos-Kudła B., Siemińska L., Londzin-Olesik M., Głogowska-Szeląg J., Nowak W., Kajdaniuk D. Optimization of the treatment of moderate to severe and active thyroid orbitopathy considering the recommendations of the European Group on Graves' Orbitopathy (EUGOGO). Endokrynol Pol. 2022. № 73(4). C. 756-777. DOI: 10.5603/EP.a2022.0040.

4. Gunn A.H., Frisco N., Thomas S.M., Stang M.T., Scheri R.P., Kazaure H.S. Patient-Reported Outcomes Following Total Thyroidectomy for Graves' Disease. Thyroid. 2022. № 32(1). P. 54-64. DOI: 10.1089/thy.2021.0285.

5. Report "On the state of sanitary and epidemiological well-being of the population in the Voronezh region in 2021" – Voronezh: Office of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare in the Voronezh Region, 2022. 190 p. URL: https://36.rospotrebnadzor.ru/documents/dir/24578 (date of access: 01.11.2022).

6. Petunina N.A., Martirosyan N.S., Trukhina L.V., Goncharova E.V., Telnova M.E., Saakyan S.V., Panteleeva O.G. Possibilities of predicting the course of endocrine ophthalmopathy. Effective pharmacotherapy. 2020. V. 16. № 36. S. 8-11. DOI: 10.33978/2307-3586-2020-16-36-8-11.

7. Bartalena L., Baldeschi L., Boboridis K., Eckstein A., Kahaly G., Marcocci C., Perros P., Salvi M., Wiersinga W. European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for te Management of Graves' Orbitopathy. Eur Thyroid J. 2016. № 5. C. 9–26. DOI: 10.1159/000443828.

8. Sviridenko N.Yu., Bessmertnaya E.G., Belovalova I.M. Mikheenkov A.A., Sheremeta M.S., Nikankina L.V., Malysheva N.M. Autoantibodies, immunoglobulins and cytokine profile in patients with Graves' disease and endocrine ophthalmopathy. Problems of Endocrinology. 2020. № 66 (5). P. 15-23. DOI: 10.14341/probl12544.

9. Zuhur S.S., Bilen O., Aggul H., Topcu B., Celikkol A., Elbuken G. The association of TSH-receptor antibody with the clinical and laboratory parameters in patients with newly diagnosed Graves' hyperthyroidism: experience from a tertiary referral center including a large number of patients with TSH-receptor antibody-negative patients with Graves' hyperthyroidism. Endocrynol Pol. 2021. № 72(1). P. 14-21. DOI: 10.5603/EP.a2020.0062.

10. Jeon H., Lee J.Y., Kim Y.J., Lee M.J. Clinical relevance of thyroid-stimulating immunoglobulin as a biomarker of the activity of thyroid eye disease. Eye (2022). DOI: 10.1038/s41433-022-01981-z.

11. Nicolì F., Lanzolla G., Mantuano M., Ionni I., Mazzi B., Leo M., Sframeli A., Posarelli C., Maglionico M.N., Figus M., Nardi M., Marcocci C., Marinò M. Correlation between serum anti-TSH receptor autoantibodies (TRAbs) and the clinical feature of Graves' orbitopathy. J Endocrinol Invest. 2021. № 44(3). P. 581-585. DOI: 10.1007/s40618-020-01353-y.

12. Lat A.M., Jauculan M.C., Sanchez C.A., Jimeno C., Sison-Peña C.M., Pe-Yan M.R., Pagkatipunan P.M., Suller A., Cena M. Risk Factors Associated with the Activity and Severity of Graves' Ophthalmopathy among Patients at the University of the Philippines Manila-Philippine General Hospital. ASEAN Fed Endocr Soc. 2017. № 32(2). P. 151-157. DOI: 10.15605/jafes.032.02.09.

13. Nabi T., Rafiq N. Factors associated with severity of orbitopathy in patients with Graves' disease. Taiwan J Ophthalmol. 2020. V. 4. № 10(3). P. 197-202. DOI: 10.4103/tjo.tjo_10_20.

14. Stöhr M., Oeverhaus M., Lytton S.D., Horstmann M., Zwanziger D., Möller L., Stark A., Führer-Sakel D., Bechrakis N., Berchner-Pfannschmidt U., Banga J.P., Philipp S., Eckstein A. Predicting the Relapse of Hyperthyroidism in Treated Graves' Disease with Orbitopathy by Serial Measurements of TSH-Receptor Autoantibodies. Horm. Metab. Res. 2021. V. 53(4). P. 235-244. DOI: 10.1055/a-1373-5523.