AUTOIMMUNE AND HEMATOLOGICAL STATUS OF GRAVES' DISEASE PATIENTS

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The authors declare that they have no conflicts of interest

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Grave's disease, autoimmune disorders, anemia, rates of severity of anemia, morphological types of anemia.

Abstract

Purpose of the study: *comparative assessment of hematological and autoimmune status of patients with Graves' disease (GD).*

Materials and methods. *43 GD patients aged between 19 and 64 years, 26 of which were women and 17 were men, have been examined. Assessment of hemograms of examined patients helped to reveal anemia in 28(65.1%) examined patients (group I). In 15 (34.9%) patients (group II) anemia was not detected. Mild anemia was diagnosed in 25 (89.3%), moderate anemia – in 3 (10.7%) patients. Hemoglobin, hematocrit, erythrocyte count and erythrocyte indices MCV, MCH, MCHC, serum Fe and ferritin status was chaecked in clinical analysis. The immune status was assessed by the level of CD3+, CD4+, CD8+, CD19+, CD4+/CD8+, CEC, Ef, TSHRAb and hormonal status by the level of TSH, T4 free.*

Results. *Microcytic anemia was determined in 15 (53.6%) patients, normocytic - in 12 (42.8%), macrocytic - in 1 (3.5%) patient due to volume of erythrocytes' MCV. According to morphological criteria of MCH (mean content of hemoglobin in erythrocyte) anemia hypochromic type of anemia was noted in 15 (53.6%) patients, normochromic - in 12 (42.8%), hyperchromic - in 1 (3.5%) patient. In 15 (53.6%%) patients in the group I microcytic - hypochromic anemia was diagnosed, which is characteristic for iron-deficient anemia; in 12 (42.8%) patients was verified normocytic-normochromic anemia, which has morphological parameters of anemia of chronic diseases and in 1 (3.5%) patient macrocytic-hyperchromic anemia.*

Comparative assessment of HGB level and indicators of iron metabolism in GD patients with anemia detected decreasing of HGB by 20%, serum Fe by 20%, ferritin by 29% compared to the corresponding control values. More pronounced depletion of the iron depot (ferritin) due to the fact that the development of anemia is preceded by a "latent iron deficiency", an indicator of which is ferritin.

Conclusions. *GD is characterized by high frequency of anemia (65.1%), mostly mild form (89.3%), microcytic-hypochromic (53.6%), characteristic of iron deficiency anemia. The severe hematological disorders, detected among GD patients with anemia are accompanied by deep autoimmune changes and hyperfunction of the thyroid gland.*

Грейвс ауруы бар науқастардың аутоиммунды және гематологиялық жағдайы

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Аңдатпа

Зерттеудің мақсаты *- Грейвс ауруы (ГА) бар науқастардағы гематологиялық және аутоиммундық жағдайды салыстырмалы бағалау.*

Материал және әдістер. *19 жастан 64 жасқа дейінгі ГА бар 43 адам тексерілді. Олардың ішінде 26 әйел, 17 ер адам бар. Тексерілген пациенттердің гемограммасын бағалау 28 (65,1%) адамда (1-топ) анемияны анықтады. 15 (34,9%) науқастарда (2-топ) анемия байқалмады. Жеңіл дәрежелі анемия 25 (89,3%), орташа дәрежеде - 3 (10,7%) науқастарда байқалды. Клиникалық қан анализінде гемоглобин, гематокрит, эритроциттер саны және MCV, MCH, MCHC, Сарысу Fe және ферритиннің эритроциттік индекстері анықталды. Иммундық мәртебе CD3+, CD4+, CD8+, CD19+, CD4+/ CD8+, ОСК, Эф, TSHRAb*

деңгейлері бойынша бағаланды. Гормоналды күй - TSH, T4 free деңгейінде.

Нәтижелер. *MCV эритроциттерінің көлемі бойынша микроциттік анемия 15 (53,6%), нормоцитарлы – 12 (42,8%), макроциттік – 1 (3,5%) науқаста анықталды. MCH анемиясының морфологиялық көрсеткіші бойынша (эритроциттегі гемоглобиннің орташа мөлшері) анемияның гипохромды түрі 15 (53,6%), нормохромды – 12 (42,8%), гиперхромды – 1 (3,5%) науқаста байқалды. 1-ші топтағы науқастардың 15-інде (53,6%) темір тапшылығы анемиясына тән микроцитарлы-гипохромды анемия байқалды, 12 (42,8%) науқастарда созылмалы аурулар анемиясының морфологиялық параметрлері бар нормоцитарлы-нормохромды анемия және 1 (3,5%) науқаста макроцитарлы-гиперхромды анемия верификацияланды.*

Анемиясы бар ГА бар емделушілерде HGB деңгейі мен темір алмасуының көрсеткіштерін салыстырмалы бағалау тиісті көрсеткіштермен салыстырғанда HGB 20% - ға, сарысулық Fe 20%-ға, ферритиннің 29%-ға төмендегенін анықтады. Темір қоймасының (ферритин) неғұрлым айқын сарқылуы анемияның дамуының алдында "жасырын темір тапшылығы" болатындығына байланысты, оның көрсеткіші ферритин болып табылады.

Қорытындылар. *BG анемияның жоғары даму жиілігімен сипатталады (65,1%), көбінесе жеңіл дәрежеде (89,3%), темір тапшылығы анемиясына тән микроцитарлы-гипохромды (53,6%). Анемиясы бар ГА бар адамдар тобында анықталған айқын гематологиялық бұзылулар терең аутоиммунды өзгерістермен және қалқанша безінің гиперфункциясымен қатар жүреді.*

Аутоиммунный и гематологический статус пациентов с болезнью Грейвса

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Аннотация

Цель исследования *– сравнительная оценка гематологического и аутоиммунного статуса у пациентов с болезнью Грейвса.*

Материал и методы. *Обследовано 43 лица с БГ в возрасте от 19 до 64 лет. Среди них 26 женщин, 17 мужчин. Оценка гемограммы обследованных пациентов выявила анемию у 28 (65,1%) лиц (1-ая группа). У 15 (34,9%) больных (2-ая группа) анемия не наблюдалась. Анемия легкой степени отмечалась у 25 (89,3%), средней степени тяжести - у 3 (10,7%) больных. В клиническом анализе крови определяли гемоглобин, гематокрит, количество эритроцитов и эритроцитарные индексы MCV, MCH, MCHC, сывороточное Fe и ферритин. Иммунный статус оценивали по уровню CD3+, CD4+, CD8+, CD19+, CD4+/ CD8+, ЦИК, Эф, TSHRAb. Гормональный статус – по уровню TSH, T4 free.*

Результаты. *По объему эритроцитов MCV микроцитарная анемия определялась у 15 (53,6%), нормоцитарная – 12 (42,8%), макроцитарная – 1 (3,5%) пациента. По морфологическому показателю анемии MCH (среднее содержание гемоглобина в эритроците) гипохромный тип анемии отмечался у 15 (53,6%%), нормохромный – 12 (42,8%), гиперхромный – 1 (3,5%) больного. У 15 (53,6%%) пациентов 1-ой группы отмечалась микроцитарно - гипохромная анемия, что характерно для железодефицитной анемии, у 12 (42,8%) больных верифицирована нормоцитарно-нормохромная анемия, имеющая морфологические параметры анемии хронических заболеваний и у 1 (3,5%) больного макроцитарно-гиперхромная анемия.*

Сравнительная оценка уровня HGB и показателей обмена железа у пациентов с БГ с анемией выявила снижение HGB на 20%, сывороточное Fe на 20%, ферритина на 29% в сравнении с соответствующими контрольными показателями. Более выраженное истощение депо железа (ферритин) связано с тем, что развитию анемии предшествует «латентный дефицит железа», показателем которого является ферритин.

Выводы. *БГ характеризуется высокой частотой развития анемии (65,1%), чаще легкой степени (89,3%), микроцитарно-гипохромной (53,6%), характерной для железодефицитной анемии. Выявленные в группе лиц с БГ с анемией выраженные гематологические нарушения сопровождаются глубокими аутоиммунными изменениями и гиперфункцией щитовидной железы.*

Конфликт интересов: *Авторы заявляют об отсутствии конфликта интересов*

Ключевые слова: *болезнь Грейвса, аутоиммунные нарушения, анемия, степень тяжести анемии, морфологические типы анемии.*

Relevance

Although more than 100 years have passed since the first description of autoimmune thyroiditis in 1912 by the Japanese physician Hashimoto Hakaru, and nearly 200 years since the publication of the world-famous article "Palpitation with enlarged thyroid gland" by the Dutch physician Robert James Graves in 1835, nevertheless mechanisms of autoimmune diseases of the thyroid gland (TG) are still not fully studied [1, 2, 3]. Currently, both the Grave's disease and autoimmune thyroiditis (AIT) are considered as the classic organ-specific autoimmune diseases [4, 5]. Scientists have paid attention to relationship between the autoimmune process in the thyroid gland and hematological diseases only in recent decades. The risk of anemia in autoimmune diseases of the thyroid gland may be due to pernicious anemia and atrophic gastritis, celiac disease, autoimmune hemolytic syndrome, celiac disease or rheumatic diseases [6, 7, 8, 9]. Few studies dedicated to identifying of link between anemia and thyroid disease show contradictory results regarding the incidence of anemia in hyperthyroidism. Some scientists revealed anemia in 30,2%-40.9% of patients with hyperthyroidism [10], others – in 17.9% [11], thirds – in 2,8% [12]. The literature data on types of anemia in hyperthyroidism also are contradictory [10, 13].

Although influence of excess thyroid hormones is well-known fact, the exact pathogenesis of GD anemia remains unclear [14, 15]. Along with this, some authors found that even against the background of euthyroidism there is a significant positive relationship between the level of free thyroid hormones, hemoglobin and the level of erythrocytes, conducting large cohort studies [16, 17]. M'Rabet-Bensalah K. et al (2016) determined that only in 5% of cases anemia is associated with TG hormonal imbalance [11].

Suggested causes of anemia in hyperthyroidism are stimulation of erythropoiesis by thyroid hormones, causing bone marrow hypoplasia, decreasing of mean content volume (MCV), hematopoietic stem cell dysfunction (such as myelodysplasia), shortened lifespan of red blood cells, and inefficient use of iron [6, 18, 19].

Thus, anemia in patients with DG is multifaceted process, the mechanisms of which are not yet fully studied. Mutually aggravating course of anemia and GD is a clinical problem.

Purpose of the study – comparative assessment of hematological and autoimmune status of patients with Graves' disease.

Materials and methods

43 GD patients, underwent surgery in the department of endocrine surgery of Scientific Center of Surgery named after M.A.Topchubashov, aged between 19 and 64 years, including 26 women and 17 men, have been observed. Assessment of hemograms of examined patients helped to detect the anemia in 28 (65.1%) examined patients (group I). In 15 (34.9%) patients (group II) anemia was not detected. Mild anemia was detected in 25 (89.3%), moderate anemia – in 3 (10.7%) patients. Hemoglobin and erythrocyte indices MCV (mean erythrocyte volume), MCH (mean HGB content in erythrocyte), MCHC (mean concentration of HGB in erythrocyte mass) were checked in clinical analysis. Additionally, the levels of serum iron (Fe-ser) and ferritin (Fr) were determined (Roche kit).

Anemia was diagnosed at a hemoglobin level of 120 g/l or less in women and 130 g/l or less in men (WHO, 2001). Phenotyping of blood lymphocytes was conducted by means of fluorescent microscope for markers CD3+ (total population of T-lymphocytes), CD4+ (T-helpers), CD8+ (T-cytotoxic suppressors), CD19+ (B-lymphocytes) (panel LLC-Sorbent, Moscow) and results were accounted as %. The content of the CEC in the blood serum was carried out according to the method of Yu.A. Grinevich, A.N. Alferov, 1981, in modification [20]. Well-known method for studying peripheral blood, the Zinkham-Conley method, modified by E.N. Novoselova was used for determining of erythrophagocytosis in blood plasma [21]. The level of hormones TSH and T4 free (set by Roche) and antibodies to the TSH receptor (TSHRAb) also were detected (set by Roche). Mathematical analysis of achieved results was conducted using the Excel 2017 software package. The structural characteristics of the variational series (mean, error of the mean), and to assess the differences between the samples, the nonparametric Wilcoxon-Mann-Whitney test also was used [22].

Results and discussion

According to the volume of erythrocytes (MCV) microcytic anemia was determined in 15 (53.6%) patients, normocytic - in 12 (42.8%), macrocytic - in 1 (3.5%) patient. According to morphological indicators of anemia hypochromic type of anemia MCH was noted in 15 (53.6%), normochromic - in 12 (42.8%), hyperchromic – in 1 (3.5%) patient. In 15 (53.6%) patients of group I they found microcytic - hypochromic anemia, which is characteristic for iron deficiency anemia, normocytic-normochromic anemia, which has morphological parameters of anemia of chronic diseases was verified in 12 (42.8%) patients and 1(3.5%) patient had macrocytic-hyperchromic anemia.

Table 1.
Hemogram of patients with DG before surgery (M±m)

Indicator		Almost healthy (n=15)	GD with anemia (n=28)	GD without anemia (n=15)	"All patients" with GD (n=43)
HGB, g/l	Hemoglobin concentration	133.2±1.8	107.2±1.6* *	132.7±2.6^	116.3±2.4*
RBC x 10^{12}/l	RBC count	4.3±0.07	4.4±0.1	4.8±0.1*^	4.6±0.08*
HCT, %	Hematocrit	39.8±0.5	33.0±0.4* *	39.8±0.8^	35.3±0.6*
CI	Color indicator	0.92±0.006	0,77±0,01*	0,82±0,02*	0,79±0,01*
MCV, fl	Mean volume of erythrocyte	91.9±0.6	75.8±1.7*	82.5±1.5*^	77.9±1.4*
MCH, pg	Average content of HGB in erythrocyte	30.8±0.2	25.6±0.6*	27.7±0.6*^	26.3±0.4*
MCHC, g/dl	Mean concentration of HGB in erythrocyte mass	33.4±0.04	33.6±0.05	33.3±0.3	33.6±0.1
Fe-ser., mmol/l	Serum iron content	18.4±1.3	14.7±0.3* *	16.0±0.5^	15.5±0.5*
Fr, ng/ml	Ferritin	35.9±2.0	25.5±1.8*	33.0±1.1^	28.1±1.3*

Note: * - statistical significance of differences relative to data in practically almost healthy people; ^ - statistical significance of differences between groups of patients with and without anemia; * - statistical significance of differences between groups of patients with anemia and "all patients"

As it is seen on the Table 1, HGB level, color score, mean erythrocyte volume, mean erythrocyte HGB, serum iron, ferritin in pre-surgery period in the group "all patients" (n=43) statistically significantly lower than the corresponding indicators of the control group, and mean concentration of HGB in erythrocytes practically does not differ from the norm. The given violations are mostly associated with changes in patients of the group I. Changes of all indicators in this group of patients have more pronounced character in comparison with the group "all patients" on three indicators such as HGB, hematocrit and serum iron levels, which significantly different from each other (p<0.05). All indicators of patients in group I, except MCHC, significantly different from corresponding indicators of the 2nd group. Aa a result of assessment of HGB level and iron metabolism indicators authors determined in patients of group I decrease in HGB by 20%, serum Fe by 20%, ferritin by 29%, compared to control indicators (Table 1). More pronounced iron depletion (ferritin) is related with the fact that the development of anemia is preceded by a "latent iron deficiency", an indicator of which is ferritin. Only the number of erythrocytes, the color index, the average volume of erythrocytes and the average content of hemoglobin in erythrocytes are significantly reduced in comparison with the control indicators (p<0.05) in patients of group II (p<0,05).

Table 2.
Immunogram of persons with GD before surgery (M±m)

Indicators	Almost healthy (n=15)	GD with anemia (n=28)	GD without anemia (n=15)	GD "all patients" (n=43)
CD3+, %	66,5±1,4	47,8±1,1*	50,1±1,3*	48,8±0,8*
CD4+, %	37,9±0,9	30,2±0,6*	29,8±0,9*	30,0±0,5*
CD8+,%	28,3±0,8	18,5±0,4*	19,9±0,6*	19,0±0,4*
CD4+/CD8+	1,4±0,04	1,6±0,03*	1,5±0,04^	1,6±0,02*
CD19+,%	11,3±0,6	18,6±0,5*	17,8±0,6*	18,4±0,4*
CIC, r.u.	64,3±1,5	98,2±1,7*	77,0±1,8*^	86,5±2,2*
FU, %	0,8±0,08	2,5±0,3*	1,2±0,08*^	2,1±0,2*

Note: * - statistical significance of differences relative to data in practically almost people: ^ - statistical significance of differences between groups of patients with and without anemia

Immunological disorders, detected in patients, are associated with the etiology and pathogenesis of GD. The values of indicators of the group "all patients", the 1st and 2nd groups (except the immunoregulatory index of the 2nd group) differ from control indicators (p<0.05) (Table 2). Comparative evaluation of immunograms of patients of the 1st and 2nd groups revealed more profound changes in patients with GD with anemia according to three indicators of autoimmunity (CD4+/CD8+, CIC, FU) which statistically differ from indicators of GD patients without anemia.

Table 3.
Levels of TSHRAb, TSH and T4 free in GD patients before surgery (M±m)

Parameters	TSHRAb	TSH	T4 free
All patients (n =43)	10,8±0,8*	0,1±0,01*	16,9±2,9*
GD with anemia (n =28)	10,9±1,0*	0,1±0,02*	13,9±2,5*
GD without anemia (n =15)	10,6±1,3*	0,1±0,03*	22,4±7,1*
Norm	<1,75 – negative >1,75 – positive (IU/l)	0,32-5,2(mIU/l)	0,7-1,8(ng/dl)

Note: * - statistical significance of differences compared to the norm

Studying of hormone levels and antibodies to the TSH receptor also revealed changes characteristic for GD. The level of antibodies to the TSH receptor is significantly increased compared to the norm in all groups and T4free level, and the TSH level is significantly lower in comparison with the norm (Table 3).

Conclusion

GD is characterized by high frequency of development of anemia (65.1%), mostly the mild form (89.3%), and microcytic-hypochromic (53.6%), characteristic for iron deficiency anemia.

The comparative assessment of HGB level and indicators of iron metabolism in GD patients with anemia has revealed decreasing of HGB by 20%, serum Fe by 20%, ferritin by 29% compared to the corresponding control values. A more pronounced depletion of the iron depot (ferritin) is associated with the fact that the development of anemia is preceded by a "latent iron deficiency", an indicator of which is ferritin.

Diagnosing of severe hematological disorders in group of GD patients with anemia are accompanied by deep autoimmune changes and hyperfunction of the thyroid gland.

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