

## HLA antigens and the distribution of the lymphocytes in Georgian population Graves' disease

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### ABSTRACT

A total 128 patients of Georgian population with Graves' disease were examined. Standard microlymphocytotoxic test with HLA typing serri was used for HLA typing. The existence of the association between HLA antigens and the investigated disease was determined by relative risk (RR). The increase of the relative risk more than "2" was already important. To determine the distribution of the lymphocytes' subpopulations between the regional artery-vena and the elbow vena-finger blood systems the blood was taken from 80 patients during the operation. The lymphocytes' subpopulations were determined in all patients using monoclonal antibodies anti - CD3+, - CD4+, - CD8+, - CD19+, - CD25+, - CD35+, - CD16+56+. HLA DR3 antigen was determined in 56% patients with RR 4,5. So, HLA DR3 is considered to be the marker of Graves' disease in Georgian population. At the same time a decrease in the frequency of HLA B7DR2 was found. The gaploptype HLA B7DR2 is considered to carry "protective" properties in Georgian population with Graves' disease. The amount of CD19+ cells are increased in the regional artery in comparison with the regional vena and the elbow vena blood systems. It is supposed, that CD19+ cells infiltrate the thyroid gland or experience unknown changes. The relative and absolute amounts of CD25+ CD35+ cells were statistically reliably increased in the regional vena in comparison with the regional artery and the elbow vena blood systems, so CD25+, CD35+ cells are dropped out of the defeated area.

**KEYWORDS:** HLA antigens, Graves' disease, Georgian population, thyroid gland

**G**raeves' disease – (diffuse toxic goiter) is an autoimmune disease caused by output of antibodies to thyrotropic hormone receptors, clinically manifestation as hyperthyroidism syndrome coupled with extrathyroid pathology (endocrine ophthalmopathy, pretibial myxedema, acropathy) [1,7].

Graves' disease is the multifactorial disease, due to which genetic particularities of immune response are realized together with environmental factors. Emotional and stress factors assist the realization of hereditary predisposition. In result, autoreactive lymphocytes (CD4+, CD8+ lymphocytes, B-lymphocytes) infiltrate thyroid gland tissue [8].

Genetic factors play important role in the development of the disease. Besides, much earlier researches revealed the association of HLA antigens with Graves' disease development [2,5].

HLA antigens are located on the short shoulder of the 6<sup>th</sup> chromosome. The first class molecules (HLA A, HLA B, HLA C) are expressed practically on every body cells and contain one heavy and one light polypeptide chains [10].

The second class molecules (HLA D region) contain three loci (DR, DQ, DP). They are expressed only on B-lymphocytes [5]. MHC has important biological functions. The main role of HLA antigens is to determine hereditary predisposition to several diseases [8].

The practical meaning of the works, studying the association of the HLA genes with diseases concludes in typing population. As a result, the high risk groups will be revealed and prevention measures carried on. Besides, HLA antigens typing may be used as additional diagnostic test for preliminary diagnostics of disease and it's prevention [1,8].

### MATERIALS AND METHODS

28 patients out of Georgian population carrying Graves' disease were the objects of the investigation.

The diagnosis was confirmed clinically and laboratory.

Standard microlymphocytotoxic test with HLA typing serri was used for HLA typing.

Antigen frequency was determined according to formula  $F=n/N$  (n – antigen carriers; N – investigated population). The existence of the association between HLA antigens and the investigated disease was determined by relative risk (RR). The increase of the relative risk more than "2" was already important.

To determine the distribution of the lymphocytes' subpopulations between the regional artery-vena and the elbow vena-finger blood systems the blood was taken from 80 patients during the operation.

The lymphocytes' subpopulations were determined in all patients using monoclonal antibodies anti - CD3+, - CD4+, - CD8+, - CD19+, - CD25+, - CD35+, - CD16+56+.

The results were elaborated according to variation statistic methods ( $p<0,05$ ).

### RESULTS AND DISCUSSIONS

HLA DR3 antigen was determined in 56% of patients with Graves' disease (compared to 21% in the control group) with RR - 4,5.

Traditionally, DR3 antigen is the marker of many autoimmune diseases [4,5,8].

Besides, the frequency of gaploptype A1B8 was increased: HLA A1 antigen was determined in 17% of patients with RR 1,94 against - 9,7% in the control group. HLA b\* antigen was determined in 14% of patients with RR 1,91 – against - 8,13% in the control group.

The antigen frequency increasing for HLA A1B8 gaploptype is especially important, as Georgian population is characterized by lower frequency of these traditional markers of high immunoreactivity [1].

At the same, the "protective" antigens, such as the gaploptype HLA B7DR2 were found with decreased frequency.

The antigen frequency for HLA B7 was 10,9% in patients – against 14,43% in the control group, with RR 0,73. The frequency of HLA DR2 antigen was 23% in patients against 27,63% in the control group, with RR – 0,73.

These persons carrying these antigens have lower risk of the Graves' disease development.

The results, which were totally different from the control group were statistically reliable. In the control group were used the HLA antigens spread among Georgian population researched by N.Makhatadze [1] (Tab.1).

The studies of the lymphocytes' subpopulation distribution between the regional artery-vena and the elbow vena-finger blood systems revealed the increase of CD19<sup>+</sup> cells amount in the regional artery in compared to the regional vena.

The relative and absolute amounts of CD19<sup>+</sup> cells in the regional artery (451±262 – 29%±11%) is statistically

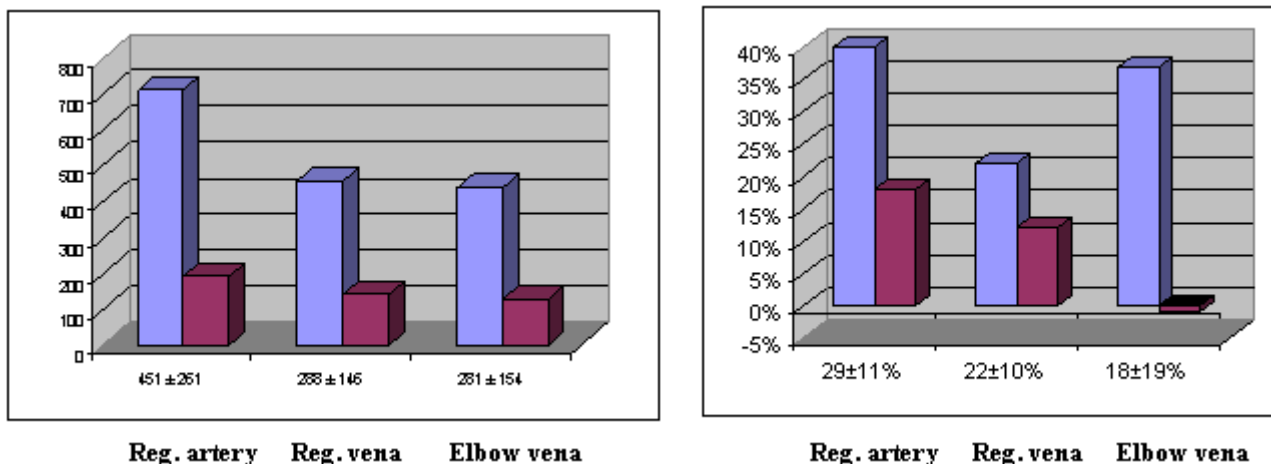
reliably increased in comparison with regional vena (288±146 – 22%±10%) and the elbow vena (281±154 – 18%±9%), p<0,05 (Fig.1).

It is supposed, that CD19<sup>+</sup> cells infiltrated the thyroid gland or experience there unknown changes [7,9].

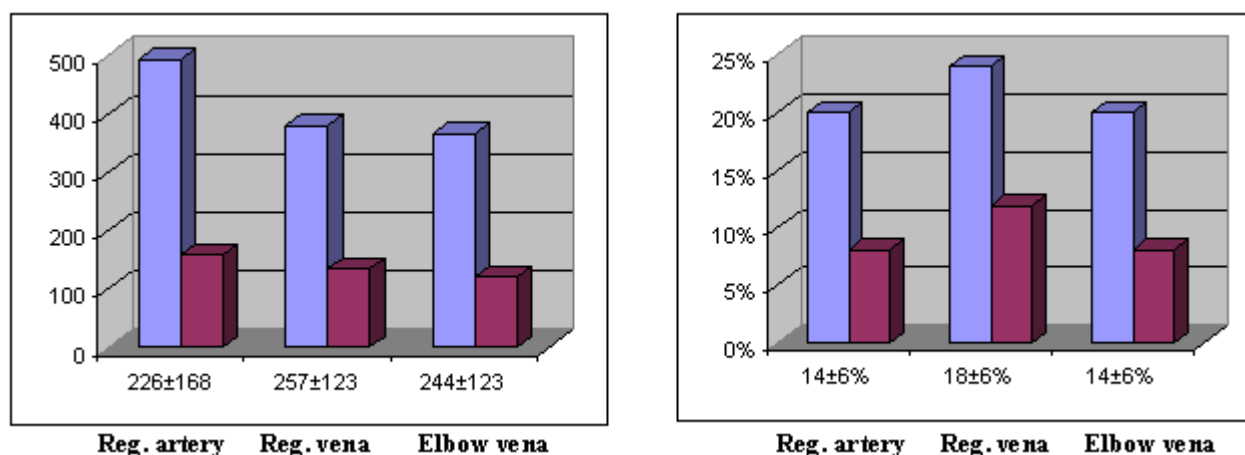
The relative and absolute amounts of CD25<sup>+</sup>, CD35<sup>+</sup> cells were statistically reliably increased in the regional vena in comparison with the regional artery and the elbow vena (266±166 – 14%±6% in the regional artery), (257±129 – 18%±6% in the regional vena), (244±129 – 14%±6% in the elbow vena) (Fig.2).

HLA antigens	Patients (n=128)		Control group %	P	RR
	abs.	%			
A 1	22	17	9,76	< 0,05	1,94
A 2	72	56,3	57,32	< 0,05	0,96
A 3	26	20	22,36	< 0,05	0,86
A 9	30	23	25,81	< 0,05	0,86
A 10	24	18	16,46	< 0,05	1,15
B 5	42	33	33,74	< 0,05	1,03
B 7	14	10,9	14,43	< 0,05	0,72
B 8	19	14,6	8,13	< 0,05	1,96
B 15	18	14	8,13	< 0,05	1,8
B 35	28	21	26,89	< 0,05	0,76
DR 1	26	20	15,79	< 0,05	1,3
DR 2	30	23	27,63	< 0,05	0,78
DR 3	70	54	21,05	< 0,05	4,5
DR 4	24	18,7	21,71	< 0,05	0,83
DR 5	44	34	23,68	< 0,05	1,66
DR 7	18	14	16,46	< 0,05	1,2

**Tab.1** Spreading of the HLA A, B, DR antigens among patients and control group in Georgian population with Graves' disease.



**Fig.1** The distribution of CD19<sup>+</sup> cells' in patients of Georgian population with the Graves' disease.



**Fig.2** The distribution of the CD25<sup>+</sup>, CD3<sup>+</sup> lymphocytes in patients of Georgian population with the Graves' disease.

CD25<sup>+</sup>, CD35<sup>+</sup> cells amounts in the thyroid gland is considerably higher, than in the circulation, so these cells are dropped out of the defeated area.

The peripheral blood measure shows statistically reliable increase of the relative and absolute amounts of CD8<sup>+</sup> cells (cytotoxic/suppressive cells) and NK cells (CD16<sup>+</sup>56<sup>+</sup>).

The amounts of the CD8<sup>+</sup> cells in the patients were 23% ± 1,8% (p < 0,1) – against 30,1% ± 1,9 in the control group. CD16<sup>+</sup>56<sup>+</sup> cells in the patients were 11,9% ± 1,4% (p < 0,05) – against 17,84% ± 2,36% in the control group.

The levels of the other types of lymphocytes didn't show difference from the control group.

### CONCLUSION

A total 128 patients of Georgian population with Graves' disease were examined

HLA DR3 antigen was determined in 54% of patients with relative risk 4,5. So, HLA DR3 is considered to be the marker of Graves' disease in Georgian population.

At the same time a decrease in the frequency of HLA B7DR2 was found. The haplotype HLA B7DR2 is considered to carry "protective" properties in Georgian population with Graves' disease.

The amount of CD19<sup>+</sup> cells are increased in the regional artery in comparison with the regional vena and the elbow vena blood systems. It is supposed, that CD19<sup>+</sup> cells infiltrate the thyroid gland or experience unknown changes.

The relative and absolute amounts of CD25<sup>+</sup> CD35<sup>+</sup> cells were statistically reliably increased in the regional vena in comparison with the regional artery and the elbow vena blood systems, so CD25<sup>+</sup>, CD35<sup>+</sup> cells are dropped out of the defeated area.

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## Антигены системы HLA и динамика перераспределения иммунокомпетентных клеток при диффузном токсическом зобе в грузинской популяции

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### Р Е З Ю М Е

Обследованы лица грузинской национальности с диффузным токсическим зобом. 128 больным проведено типирование по HLA, а у 80 больных изучено перераспределение субпопуляций лимфоцитов между системами: регионарная артерия – регионарная вена щитовидной железы, локтевая вена – палец. Статистически достоверная ассоциация с диффузным токсическим зобом выявление для HLA DR3 у 54% больных, против 21% в контрольной группе, RR=4,5, а отрицательная – с антигенами HLA DR2 (RR=0,78) и HLA B7 (RR=0,72). Таким образом, антиген HLA DR3, традиционный маркер целого ряда аутоиммунных заболеваний, является антигеном предрасположенности к диффузному токсическому зобу в грузинской популяции, а гаплотип HLA B7DR2 следует считать носителем «протекторных» свойств, фактором низкой иммунореактивности для лиц данной популяции. При перераспределении иммунокомпетентных клеток между системами: регионарная артерия – регионарная вена, локтевая вена – палец, отмечено статистически достоверное снижение CD19+ клеток в регионарной артерии, в сравнении с регионарной и локтевой венами. По видимому, CD19+ лимфоциты инфильтрируют щитовидную железу или претерпевают в эти органе определенные изменения. Количество CD25+ CD35+ клеток в регионарной артерии статистически достоверно выше, чем в регионарной вене щитовидной железы, допускаем, что CD25+, CD35+ лимфоциты вымываются из пораженного очага.

**Ключевые слова:** антигены HLA, грузинская популяция, диффузный токсический зоб, щитовидная железа

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