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STANDARDIZATION OF HLA ANTIGENS IN JUVENILE HYPERTENSION

ABSTRACT — Within the framework of the research of juvenile hypertension the standardization of HLA antigens of A and B Loci was realized in 199 patients, within the age bracket of 14—26 years, with oscillating or permanently increased blood pressure (BP) values, and in 227 healthy, normotonic persons.

In 145 patients with occasional increase of BP above the normal standard for the age or sex, a lower frequency of HLA-B40 and B35 antigens was observed compared with the control group of healthy individuals.

In 44 people with permanently increased BP there was a conspicuously frequent occurrence of HLA-B5 antigen, and less frequent occurrence of HLA-B35 antigen.

On evaluating the two groups as a whole, in comparison with the control set, we have found higher frequency of HLA-B5 antigen and lower frequency of HLA-B8 and B35 in ill persons. Following the statistical correction of all the above-mentioned results the frequency of HLA-B35 antigen remained significantly lower, in all groups, with the lowest percentage of occurrence in patients with permanent hypertension. The paper deals also with the differences between results obtained in this study and in studies realized abroad. According to the experience of the authors the results point to probable relations between favourable prognoses of the development of BP level in carriers of HLA-B35 antigen. The standardization of HLA antigens should fulfil the function of screening method in the future, for detecting children with grave risk of the manifestation of essential hypertension in adult age.

KEY WORDS: HLA — Juvenile hypertension.

Essential hypertension is one of the gravest health problems on global scale, namely with regard to its early and late effects and to complications it causes. The high morbidity and mortality rate, especially in the industrially developed countries, focused the interest of research institutes on the problem, namely of centres dealing prevalingly with problems of etiopathogenesis. There is an increasing number of proofs that the almost imperceptible beginnings of the illness should be sought already in childhood. The present trends in medicine put the emphasis on prevention build upon the hitherto results of studies realized in a number of clinical and preclinical branches, among which human gene-

tics and immunology occupy an irreplaceable position.

One of the results of the numerous immuno-haematological studies has been the discovery of the main histocompatible human system (HLA). It is a genetic system encoding a large number of various antigens on the cell membrane (HLA — human leukocyte A). The area of the HLA system is formed by D, DR, B, C and A loci on the short arm of chromosome 6, and the antigens of the HLA system are inherited as simple codominating Mendel characters. Shortly after the discovery of the HLA system the interest of clinicians was arisen by the first reports on experimental finds of links between antigens of

the HLA system and various illnesses. The study of the above relations consists in determining the frequency of HLA antigens in ill persons, and comparing them with the frequency in healthy persons. For statistical evaluation of the results various types of tests are used: χ^2 — test, Fisher's test, calculation of relative hazard, etc. If the frequency of antigen in the ill person is significantly higher than in healthy individuals, the relation between HLA and the illness is regarded as positive, i.e. the carriers of the mentioned character have greater tendency to the given illness. Negative is the relation if the frequency of HLA antigen is lower in ill people than in healthy control persons. It is held that in this case the carriers of the character are less prone to contract the studied illness. On the basis of hitherto experimental and clinical experience we can conclude that certain antigens are related to certain type of illness. This link has been proved e.g. between allergy and HLA-B7, DR2, between rheumatic illnesses and HLA-B27, etc.

Although the hitherto observations have not explained the heart of the matter of the relation between the antigens of the HLA system and various diseases, it cannot be denied that the standardization of antigens is of practical significance. The detection of a certain antigen can fit into the mosaic of other auxiliary examination methods, i.e. it may serve as a diagnostic test, eventually it may fulfil the function of genetic screening.

The objective of this study has been to identify the relation between essential juvenile hypertension and antigens of the HLA system and to verify the utility of their standardization as a method of screening in infantile age.

MATERIAL

The set of our patients is formed by 199 asymptomatic children, adolescents and young adults, within the age bracket of 14–26 years, in which higher blood pressure (BP) was discovered by chance. All patients were subjected to a series of special examinations, and on the basis of the results secondary forms of hypertension have been excluded. According to the values of BP during a longer period the patients were divided into two groups:

1. 145 patients, in which the value of systolic pressure (BPs) and/or of the diastolic pressure (BPD) varied about the upper limit of the standard for the given age and sex.
2. 44 persons, in which the value of BPs and/or BPD was permanently above the mentioned limit. The control group is formed by 227 healthy normotonic individuals.

Long-term following of juvenile hypertonics enabled us to evaluate the development of BP with the following results:

- a) full normalization of BP occurred in 31% of patients
- b) values oscillating about the upper limit of the standard for the age and sex continued in 46% of the probands.

- c) permanent hypertension, requiring measures of regime, in many cases even medication, has developed in 23% of the examined.

METHODS

In patients with juvenile hypertension, as well as in persons belonging to the control group, 21 HLA antigens of loci A and B have been examined: A1, A2, A3, A9, A10, A11, A28, B5, B7, B8, B12, B13, B14, B15, B17, B18, B21, Bw22, B27, B35 and B40.

As the examination method a two-phase micro-lymphocytotoxic NIH test was applied. The lymphocytes were isolated above the Ficoll/Triosil gradient. The staining was realized with the help of eosine.

The frequency of HLA antigens was determined both in the ill and healthy persons and the results of three tests were compared: of χ^2 — test, direct Fisher's test, and by determining the value of relative hazard (RH).

RESULTS

Through statistical comparison of the results of the examination of 21 HLA antigens of A and B loci in persons with essential hypertension and in healthy persons we have come to the following results:

1. In persons with oscillating BP values (group I) on the basis of a hyperkinetic type of circulation the occurrence of HLA-B40 and B35 antigens was less frequent. Following the correction only the lower frequency of HLA-B35 (Table 1) was statistically more important.
2. In comparison with the control group in group II, i.e. in the group of patients with fixed hypertension, there was a conspicuously higher frequency of antigen HLA-B5, but prior to correction p only. On the other hand the significantly less frequent occurrence of antigen HLA-B35 continued also after the correction (Table 2).
3. By comparing the frequency of antigens of the HLA system in the whole group of 199 persons with abnormal BP values and in the control group of 227 healthy individuals, significantly higher frequency of antigen HLA-B5 and lower frequency of HLA-B8 and B35 antigens in the ill persons was recognized. Following the correction the significance of differences continues only for the HLA-B35 antigen (Table 3).

DISCUSSION

On evaluating the HLA antigens of the A and B loci in adolescents and young adults with occasionally or permanently increased BPs and/or BPD in all groups of the ill individuals, we have found statistically less frequently antigen HLA-B35, even following correction p , with the lowest frequency in patients with fixed hypertension. Prior to correction significant differences in off occurrence were observed

TABLE 1. Frequency of antigens of the HLA system in group I

HLA	patients n = 145	check n = 227	statistic evaluation			
	%	%	χ^2	P	Pc	RR
B40	6.90	16.74	7.64	0.006	NS	0.37
B35	6.28	22.03	17.78	0.00003	0.00063	0.32

TABLE 2. Frequency of antigens of the HLA system in group II

HLA	patients n = 44	check n = 227	statistic evaluation			
	%	%	χ^2	P	Pc	RR
B5	28.89	14.10	5.95	0.015	NS	2.48
B35	4.44	22.03	uncertain	PFischer 0.0023	0.047	0.16

TABLE 3. Frequency of antigens of the HLA system in the whole group of juvenile hypertonics

HLA	patients n = 199	check n = 227	statistical evaluation			
	%	%	χ^2	P	Pc	RR
B5	22.63	14.10	5.10	0.03	NS	1.78
B8	11.05	18.94	4.96	0.035	NS	0.53
B35	7.37	22.03	17.10	0.00004	0.00021	0.28

NS = non-significant difference

also in the HLA-B5 antigen (more often in the ill) and HLA-B8 and B40 antigens (with lower frequency in the ill). In Table 4 we present a survey of results of foreign studies of the relation between the HLA system and essential hypertension of adult persons. The above associations were statistically significant only in some cases, and before correction (Fersberg and Löw 1983, Gelsthorpe et al. 1979, Kristensen et al. 1977, Mercier and Jouve 1979, Sengar et al. 1985). In all these studies the group of examined hypertonics was substantially smaller than our group. In the available literature we have not found differences in the frequency of antigens HLA-B5, B8 and B40. In contrast to Fersberg and Löw (1983) antigen HLA-B35 occurred in our group with considerably less

frequency. In other antigens mentioned in the bibliography, we have not noticed chances in frequency in our material. These differences can be explained in two ways:

1. First by the number of examined persons in most studies it was much lower than the number of our probands (Fernandez-Cruz 1981, Fersberg and Löw 1983, Gelsthorpe et al. 1979, Mathews et al. 1976, Mercier and Jouve 1979, Sengar et al. 1985).
2. We have studied the relation between HLA and hypertension in young individuals, in which the blood pressure values have not been fully fixed. The development of BP has in our experience, a tendency to permanent hypertension only in 26% of people with oscillating BP values during the period of adolescence.

Our results point to probable connection with positive prognoses of the development of blood pressure level in carriers of antigen HLA-B35. The results concerning antigens HLA-B5, B8 and B40 non-significant following correction p , must be verified in a larger number of patients. According to our hypotheses the standardization of antigens of the HLA system will fulfil the function of a non-invasive screening in the group of children with the risk of manifesting essential hypertension in adult age.

TABLE 4. Results of foreign studies on the relation between essential hypertension of adults and the occurrence

Author	year	number of patients	increased occurrence of HLA antigens
Fernandez-Cruz	1981	85	B8, B12
Fersberg et al.	1983	32	B35, Cw4
Gelsthorpe et al.	1979	107	B12
Kristensen et al.	1977	149	B21
Mathews et al.	1976	44	B15
Sengar et al.	1985	67	B18, DR7
Shkvatsabaya et al.	1988	131	B13, Bw22

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