MYASTHENIA GRAVIS AND THE HL-A SYSTEM

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On the basis of a research on 100 patients a correlation is shown to exist between myasthenia gravis and HL-A 8.
The findings further support the supposition that myasthenia gravis should be divided into two types, respectively showing an increase of HL-A 8 and an increase of HL-A 2.

In several diseases, i.e., systemic lupus erythematosus (Dausset 1972), adult and childhood coeliac disease (Stokes et al. 1972, McNeish et al. 1973), autoimmune active chronic hepatitis (McKay and Morris 1972), and dermatitis herpetiformis (White et al. 1973), an altered distribution of HL-A antigens was shown compared to the normal population. We selected myasthenia gravis as the first disease to be studied, since a large number of well defined cases were available to us and there is none or little indication for genetic influence in this disease. The diagnosis had been confirmed in all cases by Dr. H.J.G.H. Oosterhuis from the Neurological Clinic of the University of Amsterdam.

The lymphocytes of 100 patients and their relatives were typed for HL-A with a standard lymphocytotoxicity test (NIH). The control group consisted of 533 unrelated healthy individuals (Berg-Loonen et al., in preparation). Apart from HL-A, the genetic markers of IgG and IgA and a number of red cell antigens were determined. The serum of all patients and their relatives was examined for the presence of autoantibodies to skeletal muscle, thyroid, gastric mucosa, adrenocortex, salivary ducts, smooth muscle, mithochondria, and nuclei, with the immunofluorescence technique (Feltkamp et al. 1974).

The phenotype frequencies of the different HL-A antigens in the group of patients were determined. The most deviating frequencies concerned the antigens HL-A 1 and HL-A 8. HL-A 1 was present in 55 out of the 100 patients (55%), while in the control group it was found in only 158 out of 533 persons (29.6%). This difference is significant ($P \ll 0.001$). The frequency of HL-A 8 was highly increased; 59 out of the 100 patients (59%) were positive for this antigen, whereas only 103 individuals of the control group (19.3%) were found to be positive. This difference is highly significant ($P \ll 0.001$; Table 1). These results confirm the findings of Pirskanen et al. (1972).

The frequency of the antigens HL-A 3 and HL-A 7 was decreased in the patients. After multiplying P with the number of comparisons that have been made, the difference remained significant only for the antigens HL-A 1 and HL-A 8.

Since this material consisted of the patients and their relatives it was possible to follow up gene segregation in the families.

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TABLE 1

HL-A PHENOTYPE FREQUENCIES IN PATIENTS WITH MYASTHENIA GRAVIS (N = 100) AND CONTROLS (N = 533)

	Patients	Controls	χ^2	P
First series				
HL-A 1	55	29.6	23.24	$\ll 0.001$
HL-A 3	16	31.1	8.76	< 0.005
Second series				
HL-A 7	15	29.6	7.94	< 0.005
HL-A 8	59	19.3	69.58	$\ll 0.001$

χ^2: 2 × 2 table with correction for continuity.

In view of the highly significant increase of HL-A 8 the patients with one parent heterozygous for this antigen were selected from the material (Table 2). We investigated 34 of such patients. According to the Mendelian laws of segregation and independent assortment, half of these patients (i.e., 17) are expected to be positive for the antigen HL-A 8, but we found 29 to be positive and only 5 negative, which deviation from the expectation is a considerable one. The difference is significant ($P < 0.001$). The observed HL-A 8 frequency in 88 siblings of the 34 patients did not differ from the expected. HL-A 1 and HL-A 8 are inherited at separate loci. In Caucasians this is far the most frequent haplotype and there exists a clear linkage disequilibrium for these two antigens. In the myasthenia gravis patients the haplotype HL-A 1 — HL-A 8 occurs about four times as frequently as in the normal Dutch population.

Like the frequency of HL-A 8 the frequency of HL-A 1 is also increased in these patients. It is quite well possible that the excess of both antigens represents the haplotype HL-A 1—HL-A 8. We therefore divided the 34 families into two categories: those families in which the HL-A 8 heterozygous parent possessed the haplotype HL-A 1—HL-A 8 and the families in which the heterozygous parent combined any other first series antigen with HL-A 8, and and thus possessed the haplotype non-HL-A 1—HL-A 8. From 23 patients with one parent possessing the HL-A 1—HL-A 8 haplotype, 20 received this haplotype and 3 did not. In

TABLE 2

HL-A 8 FREQUENCY IN PATIENTS WITH ONE PARENT HETEROZYGOUS FOR HL-A 8 (8/NON-8 × NON-8/NON-8)

		HL-A 8+	HL-A 8—	χ^2	P
34 patients	found	29	5	15.58	< 0.001
	expected	17	17		
88 siblings	found	42	46	0.18	> 0.7
	expected	44	44		

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the families with one parent having the haplotype non-HL-A 1—HL-A 8, 9 out of 11 patients received this haplotype. These ratios do not differ significantly ($\chi^2 = 0.15$, $0.7 > P > 0.5$). The excess of antigen HL-A 8 does not depend on the haplotype found: it may be present in the haplotype HL-A 1—HL-A 8 as well as in any other haplotype with HL-A 8. The excess of HL-A 1 is directly due to the increased frequency of HL-A 8 because of the linkage disequilibrium that exists for these two antigens (Table 3).

TABLE 3

COMPARISON BETWEEN HAPLOTYPES 1/8 AND NON-1/8

	HL-A 8+	HL-A 8—
23 patients with one parent having the haplotype 1/8	20	3
11 patients with one parent having the haplotype non-1/8	9	2
The excess of HL-A 8 in the patients represents the haplotype 1/8 as well as the haplotype non-1/8		
The significant excess of HL-A 1 is due to the linkage disequilibrium between HL-A 1 and HL-A 8		

When HL-A 1 segregates independently from HL-A 8 there is no deviation found in gene segregation. When both parents are heterozygous for HL-A 8 we find more patients homozygous for this antigen than expected from the Mendelian laws (Table 4).

TABLE 4

HL-A 8 FREQUENCY IN PATIENTS WITH BOTH PARENTS HETEROZYGOUS FOR HL-A 8 (8/NON-8 × 8/NON-8)

		8/8	8/non-8	non-8/non-8
11 patients	found	7	3	1
	expected	2.75	5.5	2.75
	$P = 0.02$ (exactly)			

There seems to be a preference in myasthenia gravis patients to be homozygous for HL-A 8.

The phenotype frequencies of the antigens HL-A 3 and HL-A 7 were decreased in the patients as compared to the control group. From gene segregation studies it appeared that this decrease is secondary due to the increased frequency of HL-A 8.

Neither the genetic markers of IgG and IgA, nor the red cell antigens revealed a correlation with myasthenia gravis as did the HL-A antigens.

In the serum of 22 patients (22%) autoantibodies to skeletal muscle were present. In 2% of their relatives these autoantibodies were also detected. Both figures are significantly higher than those found in matched controls.

When the patients are divided into two groups, one having and one lacking autoantibodies to skeletal muscle, the highly increased HL-A 8 frequency is found in the second group. Moreover, comparison of both groups revealed a high frequency of HL-A 2, a first series antigen, in the first group.

In 13 out of the 100 patients a thymoma was present. Twelve of these patients had autoantibodies to skeletal muscle in their serum. When the onset of the disease is before 40 years of age thymomas and autoantibodies to skeletal muscle are rare.

Summarizing we conclude that there exists a correlation between HL-A 8 and myasthenia gravis in a group of 100 patients. Significant deviations for the frequencies of other antigens proved to be secondary to the increase of HL-A 8. Furthermore, the findings support the supposition that myasthenia gravis should be divided into two types: type one showed an increase of HL-A 8, which was confined to those patients in whose serum no autoantibodies to skeletal muscle could be demonstrated, who did not have a thymoma, and who got the disease before their 40th year. The opposite type showed an increased frequency of HL-A 2. The results are a strong argument for a genetic influence in myasthenia gravis.

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