HL-A Frequencies in Patients with Multiple Sclerosis*

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SUMMARY: *The histocompatibility antigens (HL-A) have been determined in 100 multiple sclerosis (M.S.) patients and 143 randomly selected controls. In the M.S. group there was a statistically significant increase in the frequency of HL-A 7 and W 18 with an insignificant increase in HL-A 3. The variance from normal HL-A patterns in the M.S. population may play some role in establishing the substrate for this disease. Studies in experimental animals have shown that susceptibility to autoimmune disease and to virus infection is linked to the major histocompatibility locus. This has interesting implications for both the "slow virus" and the "autoimmune" theories of the etiology of multiple sclerosis.*

RÉSUMÉ: *Les antigènes d'histocompatibilité (HL-A) furent déterminés chez 100 patients atteints de Sclérose en Plaque (S.E.P.) et chez 143 contrôles choisis au hasard. Dans le groupe de malades porteurs de S.E.P., il y avait une augmentation statistiquement significative de la fréquence de HL-A 7 et W 18 et une augmentation non significative de HL-A 3. La variation des échantillons normaux HL-A dans la population porteuse de S.E.P. peut jouer un rôle dans l'établissement du substrat de cette maladie. Les études chez les animaux expérimentaux ont montré que la susceptibilité à la maladie autoimmune et à l'infection virale est reliée au facteur majeur d'histocompatibilité. Ceci a des implications intéressantes concernant les deux théories dans l'étiologie de la sclérose en plaque, soit celle du "virus lent" et celle d'une maladie autoimmune.*

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* This material was presented in part at the Royal College of Physicians and Surgeons (Canada) Meeting in Montreal, January 25, 1974.

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Study of the genetic control of the immune response in experimental animals has shown that the response to viral infection (Lilly, 1966), humoral and delayed hypersensitivity (McDevitt and Benacerraf, 1969), and the response to induction of autoimmune disease (Vladutiu and Rose, 1971) are genetically determined and linked closely to the major histocompatibility locus.

Williams and Moore (1973) have found that the susceptibility to production of Experimental Allergic Encephalomyelitis (EAE) in the backcross generations from the F^1 progeny of Brown Norway and Lewis rats is linked to the presences of the $H\text{-}1^1$ allele. Lewis rats are homozygous for the $H\text{-}1^1$ allele and are 100% susceptible. Brown Norway rats are H-1 homozygous and

TABLE I

COMPARISION OF OBSERVED VALUES OF HL-A FREQUENCIES

	Patients (n=100)			Controls (n=143)					
Antigen	#Pos.	#Neg.	%Pos.	#Pos.	#Neg.	%Pos.	Diff. in Per Cent	χ^2+	P
HL-A 1	35	65	35	40	103	28	7	1.0319	N.S.
HL-A 2	42	58	42	70	73	49	-7	.8863	N.S.
HL-A 3	36	64	36	35	108	24	12	3.2616	<.1>.05
HL-A 9	18	82	18	24	119	17	1	.0048	N.S.
HL-A 10	12	88	12	12	131	8	4	.5514	N.S.
HL-A 11	10	90	10	17	126	12	-2	.062	N.S.
W 28	8	92	8	10	133	7	1	.0025	N.S.
W 32	8	92	8	12	131	8	0	.0203	N.S.
W 29	5	95	5	9	134	6	-1	.0275	N.S.
W 30	6	94	6	11	132	8	-2	.0653	N.S.
HL-A 5	10	90	10	15	128	10	0	.0074	N.S.
HL-A 7	46	54	46	34	109	24	22	12.2177	<.001*
HL-A 8	26	74	26	31	112	22	4	.3784	N.S.
HL-A 12	22	78	22	41	102	29	-7	1.0231	N.S.
HL-A 13	5	95	5	12	131	8	-3	.5875	N.S.
W 5	11	89	11	19	124	13	-2	.1006	N.S.
W 27	9	91	9	6	137	4	5	1.5502	N.S.
W 14	6	94	6	10	133	7	-1	.0027	N.S.
W 15	6	94	6	17	126	12	-6	1.783	N.S.
W 17	3	97	3	14	129	10	-7	3.1988	<.1>.05
W 18	16	84	16	7	136	5	11	7.1319	<.01>.001*
W 10	12	88	12	22	121	15	-3	.3177	N.S.
W 21	7	93	7	4	139	3	4	1.5755	N.S.
W 16	2	98	2	7	136	5	-3	.6863	N.S.
W 22	3	97	3	6	137	4	-1	.0191	N.S.

+ Chi Square - using a Yates correction factor for continuity.

* Considered statistically significant.

100% resistant. Susceptibility to EAE, both clinical and pathological, segregated for the most part with the H-1[1] allele. Gasser, et al (1973) have had similar findings. These findings are important in the context of this paper since EAE is thought by some to be an experimental model for Multiple Sclerosis (M.S.).

These animal studies have been accompanied by a number of studies in humans examining the relationship between Human Histocompatibility Antigens (HL-A) and the prevalence of disease. These studies have brought to light a number of diseases, especially of the collagen disease variety, in which the HL-A antigen frequencies are at variance with the expected norm. (McDevitt and Bodmer, 1972, Schlosstein et al, 1973). Multiple sclerosis can now be added to this list. Several surveys of HL-A antigens in multiple sclerosis populations have been conducted in various parts of the world. The data from these surveys is noted in Table III. In this article we have reported HL-A antigen frequencies in a population of caucasian Canadian patients with multiple sclerosis.

METHODS

The patients were obtained from the rolls of the Multiple Sclerosis Clinic of University Hospital London, Ontario. Only patients meeting the diagnostic criteria of the Schumacher Panel (1965) for clinically definite multiple sclerosis have been tested. A total of 100 patients have been typed for HL-A antigens. One hundred and forty-three randomly selected healthy control subjects have also been tested. The results of our control series are similar to published control series.

The HL-A typing was done by a modified microdroplet lymphocyte cytotoxicity test (Mittal, et al. 1968), using the Terasaki T_4 tissue typing tray.

RESULTS

The data from tissue typing 100 M.S. patients and 143 randomly selected controls are displayed in Table I. There is a statistically significant increase from the expected norm in the frequencies of antigens HL-A 7 ($P<0.001$) and W-18 ($P<0.01$). There was a 12% increase in the occurrence of HL-A 3 in the M.S. group, but this failed to reach statistical significance. The occurrence of ABO blood groups (Table II) was as expected for the general population in both the control and M.S. groups.

TABLE II

ABO BLOOD GROUPS IN M.S., PATIENTS & CONTROLS

GROUP	% POPULATION	% CONTROLS	% M.S.
O	46	46	41
A	42	42	45
B	9	10	10
AB	3	3	4

TABLE III

Literature Summary of Frequencies of HL-A 7, 3, and W18 in Control and M.S. Populations

	HL-A 7		HL-A 3		W18	
NUMBER OF PATIENTS CONTROL / M.S.	% CONTROL	% M.S.	% CONTROL	% M.S.	% CONTROL	% M.S.
PATY et al 143/100 CANADA	24	46	25	36	5	16
JERSILD et al 958/135 DENMARK	26	39	25	36	7	9
NAITO et al 871/94 U.S.A.	23	26	23	40	7	16
BERTRAM et al 225/200 GERMANY	31	35	27	37	9	14
ARNASON et al 100/56 U.S.A.	21	39	23	43	—	—

DISCUSSION

Table III displays the data for several of the previously reported surveys of HL-A frequencies in M.S. patients. Our results are on the top line. The Danish study of Jersild et al. (1973) found increases in HL-A 7 and HL-A 3. The California study of Naito et al. (1972) found increases in HL-A 3 and W-18, while the German study of Bertrams, et al. (1972) found HL-A 3 was increased. Arnason, et al. (1974) from Boston have reported HL-A 3 and 7 as increased in M.S. patients. Jersild et al. (1973a) have also reported that there was a correlation between the presence of HL-A 3, 7, and W-18 and high serum measles antibody titre. In another paper Jersild et al. (1973b) have reported an additional study of a mixed lymphocyte determinant (LD-7a) that is linked to HL-A 7 and found in 70% of 28 randomly selected M.S. patients. Patients carrying this determinant had a significantly more rapid progression in clinical course than did LD-7a negative patients. Norris and Pietsch (1973) have recently reported that HL-A 3 and HL-A 7 are more frequently found in patients with paralytic poliomyelitis than in the normal. Animal studies have shown close linkage between the major histocompatibility locus and

https://doi.org/10.1017/S0317167100019788 Published online by Cambridge University Press

susceptibility to viral infections (Lilly, 1966) and to autoimmune disease, EAE (Williams and Moore, 1973).

Family and twin studies (MacKay and Myrianthopoulos, 1966) have shown there is an increased incidence of M.S. in families over the general population, but the concordance for monozygotic twins is no greater than for dizygotic twins. This is strong evidence against hereditary factors being primary in the etiology of M.S., but the HL-A frequencies suggest that there may be hereditary factors present that help determine susceptibility to acquiring M.S.

When taken together the following findings have interesting implications for both the "autoimmune" and the "virus" theories of the etiology of multiple sclerosis:

1. Certain histocompatibility antigens occur more frequently in the M.S. population than in the normal;
2. The occurrence of paralytic poliomyelitis may be associated with the presence of these same antigens;
3. The immune response locus and susceptibility to EAE in animals are both linked closely to the major histocompatibility locus.

Since the current theories for the etiology of M.S. include virus infection and related autoimmune phenomena, and both of these are influenced by genetic factors linked to the histocompatibility loci, it is important to pursue the relationship of the HL-A system to multiple sclerosis. We are in the process of relating the presence of HL-A antigens 3, 7, and W-18 to the clinical course of multiple sclerosis, to CSF composition and to measles antibody titres.

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