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HLA Antigens in Schizophrenia: No Difference Between Patients With and Without Evidence of Brain Atrophy

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Summary: The HLA antigens distribution was studied in 56 chronic schizophrenic in-patients with or without brain atrophy determined by CAT examination, and compared with that of 200 controls. There was no difference in the incidence of HLA-A_2 in the whole sample, and an increase in those without brain atrophy (by comparison with normal controls) failed to reach statistical significance. A decrease of Bw35 in the whole sample, more prominent in those without brain atrophy, again failed to be significant after multiplying the probability by the number of antigens studied.

Although the involvement of genetic factors, at least in chronic schizophrenia, is widely accepted, the search for genetic markers of the disease is still in progress (Turner, 1979). During the last decade the possibility that immunological mechanisms are involved in schizophrenia has stimulated workers from different countries to search for possible associations between the HLA system and various groups of patients suffering from the schizophrenic syndrome (Cazzullo *et al*, 1974; Smeraldi *et al*, 1976; McGuffin *et al*, 1978; Luchins *et al*, 1980a, 1980b). While correlations between specific HLA antigens and various types of the disease have been reported, the findings to date have not been consistent (Smeraldi *et al*, 1978; Mendlewicz *et al*, 1978).

The use of commonly accepted diagnostic criteria (McGuffin *et al*, 1978; Luchins *et al*, 1980a; Smeraldi *et al*, 1978) and the subgrouping of patients according to biological rather than poorly defined clinical parameters (Luchins *et al*, 1980a) might facilitate comparisons of more homogeneous groups, leading thus to a better understanding of the issue. Quite recently a study was carried out on these lines by Luchins *et al* (1980a), who reported that A_2 antigen was increased in a subpopulation of chronic schizophrenics without evidence of brain atrophy on CAT. They consequently speculated that possession of the A_2 antigen might be a prognostic factor for those patients (Luchins *et al*, 1980b).

These findings stimulated us to investigate the HLA system in a number of our patients diagnosed as schizophrenics by widely accepted criteria (Feighner *et al*, 1972) and divided into two distinct groups, according to the presence or absence of evidence of brain atrophy on a CAT examination.

Patients and Method

HLA antigens were determined in 56 unrelated chronic inpatients (41 men and 15 women), hospitalized in our department, and fulfilling Feighner's criteria for schizophrenia. Their mean age was 41.27 ± 1.06 years and their mean hospitalization time was 6.3 ± 0.5 years.

HLA typing was carried out according to the lymphocyte microtoxicity test (Terasaki and McClelland, 1964) for 11 HLA-A and 16 HLA-B antigens, employing a test panel of 120 antigens, at the Tissue Typing Laboratory, General Hospital of Athens. The antigen frequency was compared to that of a control group of 200 healthy Greek subjects, comparable to our sample with regard to geographic location and racial type (Renieri-Livieratou *et al*, 1979).

Computer automated tomography scans were available for all the patients. For every patient at least 12 tomographic pictures were obtained. The CT slice showing the ventricles at their largest at the level of the body of the lateral ventricles was selected. This cut, in the form of transparent film, was projected in enlargement and the areas of the lateral ventricles and intracranial space (corresponding to the area surrounded by the inner aspect of the skull) were measured, using a planimeter with tracer arm of fixed length. Each area was measured five times and the mean value was used. Ventricular-brain ratio (VBR) was determined as the ratio of ventricular to intra-

cranial area expressed as percentage. The measurements were made by the same person who was blind to clinical information about the patients. After ten days ten pictures, randomly selected, were measured again by the same person and the results were compared to those of the first assessment. Average error was less than 2 per cent.

In the present study ventricular enlargement was defined as a ventricular to brain ratio greater than 6.5, a figure selected according to the data presented by Barron *et al* (1976) who provide a nomogram of changes in ventricular size during ageing (1.8 per cent to 6.4±0.8 per cent first to sixth decade).

In 38 of the 56 patients the findings suggested evidence of brain atrophy. No significant difference in age, duration of illness or duration of hospitalization was found between the two groups (Frangos *et al*, in press). The Chi-square test, using Yate's correction for small numbers, was performed for the statistical evaluation of the data.

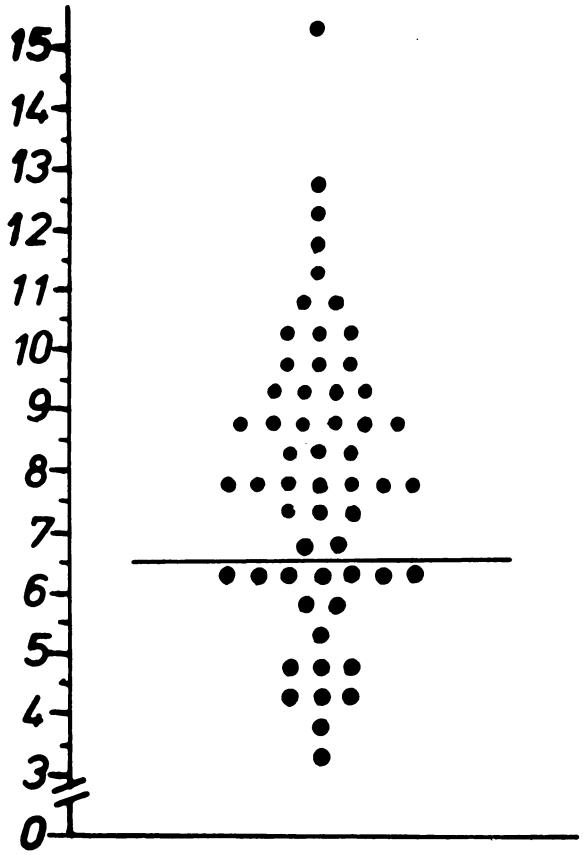

FIG 1.—Distribution of ventricular/brain ratios by CAT scan in 56 chronic schizophrenia patients. The horizontal line divides those believed to be with brain atrophy from those without.

Results

The results of our study are listed in Tables I and II.

Among the whole sample of our patients there was no difference of HLA-A_2 in comparison with the normal control group (44.6 per cent vs 45 per cent, NS).

A decrease of Bw35 was found with statistical significance in the whole sample of patients (17.8 per cent vs 36 per cent $P < 0.01$). It failed however to remain significant after multiplying the raw probability by 27, the number of antigens studied.

The distribution of the other antigens did not show any significant variation between the schizophrenics, as a whole, and the controls (Table I).

Separating the patients according to the CAT findings, Bw35, was significantly decreased in those

TABLE I

HLA antigens in all schizophrenic patients

Antigen HLA	Controls (N = 200)		Patients (N = 56)	
	n	%	n	%
A1	40	20	8	14,3
A2	90	45	25	44,6
A3	32	16	10	17,8
A9	54	27	18	32,1
A10	27	13,5	10	17,8
A11	12	6	5	8,9
A28	17	8,5	4	7,1
A29	7	3,5	1	1,8
A19.2	21	10,5	7	12,5
Aw32	24	12	9	16,1
Aw33	4	2	1	1,8
B5	66	33	20	35,7
B7	20	10	4	7,1
B8	15	7,5	5	8,9
B12	26	13	5	8,9
B13	15	7,5	3	5,4
B14	6	3	1	1,8
Bw15	5	2,5	2	3,6
Bw17	9	4,5	3	5,4
Bw18	44	22	12	21,4
Bw21	14	7	6	10,7
Bw22	19	9,5	2	3,6
Bw27	10	5	3	5,4
Bw35	72	36	10	17,8*
Bw38	7	3,5	1	1,8
Bw39	9	4,5	4	7,1
Bw40	13	6,5	7	12,5

* $P < 0.01$.

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without atrophy compared to the controls (6 per cent vs 36 per cent $P < 0.02$). This difference also failed to reach significance after multiplying by the number of antigens studied.

In the subgroup of patients without evidence of brain atrophy an increase of A_2 was found (55.6 per cent), but it failed to reach significance, nor was there a significant difference of A_2 in those with evidence of brain atrophy. No other significant differences were found between the two subgroups and the control group (Table II).

Discussion

Our findings of no significant differences in the distribution of HLA antigens, in particular A_2, between the whole sample of patients and the normal control group are in disagreement with those of Luchins *et al* (1980a) who reported a significant increase of HLA-A_2 among black schizophrenic patients, especially those without evidence of brain atrophy, and with those of Kyner *et al* (1978) who found an increase of A_2 in a white population of schizophrenics.

Although the diagnostic criteria used in our study (Feighner *et al*, 1972) are very similar to the Research Diagnostic Criteria used by others, and our patient sample, like theirs, consisted of chronic patients with poor response to neuroleptic treatment, racial differences could account for the discrepancy in the results.

Separating our patients into two subgroups, i.e., those with and those without evidence of brain atrophy, made no significant difference to the frequency of demonstration of HLA antigens, a finding against the suggestion that dividing schizophrenic patients along these lines could help reduce biological heterogeneity. Our study failed to identify a genetic marker for schizophrenia and offered no evidence for either a genetic predisposition or an immunological basis.

TABLE II

HLA antigens in schizophrenic patients with and without brain atrophy

Antigen HLA	Controls (N = 200)		Patients with brain atrophy (N = 38)		Patients without brain atrophy (N = 18)	
	n	%	n	%	n	%
A1	40	20	5	13,2	3	16,7
A2	90	45	15	39,5	10	55,6
A3	32	16	9	23,7	1	5,6
A9	54	27	11	28,9	7	38,9
A10	27	13,5	7	18,4	3	16,7
A11	12	6	3	7,9	2	11,1
A28	17	8,5	4	10,5	0	0
A29	7	3,5	0	0	1	5,6
A19.2	21	10,5	3	7,9	4	22,2
Aw32	24	12	7	18,4	2	11,1
Aw33	4	2	1	2,6	0	0
B5	66	33	11	28,9	9	50
B7	20	10	4	10,5	0	0
B8	15	7,5	4	10,5	1	5,6
B12	26	13	2	5,3	3	16,7
B13	15	7,5	0	0	3	16,7
B14	6	3	0	0	1	5,6
Bw15	5	2,5	2	5,3	0	0
Bw17	9	4,5	2	5,3	1	5,6
Bw18	44	22	11	28,9	1	5,6
Bw21	14	7	4	10,5	2	11,1
Bw22	19	9,5	1	2,6	1	5,6
Bw27	10	5	1	2,6	2	11,1
Bw35	72	36	9	23,7	1	5,6*
Bw38	7	3,5	1	2,6	0	0
Bw39	9	4,5	3	7,9	1	5,6
Bw40	13	6,5	5	13,2	2	11,1

* $P < 0.02$.

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Therefore we incline to believe that future strategy in exploring this very complex issue will be more fruitful if based on multicentred and family studies, which might reveal a more complicated relationship between HLA loci and a specific liability to the disorder, as Turner (1979) and Smeraldi *et al* (1978) recently recommended.

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