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The HLA System and Schizophrenia

A Study in a German Population

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Summary. Various diseases with a noticeable autoimmune component and frequent occurrence within one family show a statistically significant correlation with specific human leukocyte antigens (HLA). This correlation was also shown in studies of HLA in psychiatric disorders. However, results have been contradictory.

The phenotype frequencies of HLA specificities were investigated in 100 schizophrenic patients and 472 controls from the same geographic area in Germany. The frequency of HLA B27 was significantly increased in the patient group as a whole ($P = 0.017$) and in the subgroups of paranoid patients ($P = 0.005$), chronic schizophrenics ($P < 0.001$), patients with poor prognosis ($P < 0.001$), and in patients with onset of the disease before the age of 20 years ($P = 0.004$). In the latter three groups an elevated incidence of HLA A9 was also found.

The combination A9-B27 was detected in 0.63% of our control group and in 7% of the patients ($P < 0.001$). Of these patients 85.7% were chronic paranoid patients with poor prognostic features. This study gives support to the possibility of using HLA typing in genetic studies of schizophrenia, as well as in the differential diagnosis and prognosis.

Key words: Schizophrenia – HLA antigens – Psychiatric genetics – Arthropathies

Zusammenfassung. Verschiedene Erkrankungen mit offensichtlicher Beteiligung des Autoimmunesystems und gehäuftem familiärem Vorkommen weisen eine Korrelation mit spezifischen Human Leukocyte Antigens (HLA) auf. Eine solche Korrelation ergab sich auch zwischen HLA und psychiatrischen Erkrankungen. Allerdings sind die bisher gewonnenen Ergebnisse widersprüchlich.

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In vorliegender Studie wurden 100 Schizophrene und 472 Kontrollpersonen aus Mannheim auf ihr HLA-Muster untersucht. In der Gesamtgruppe der Schizophrenen fanden wir eine erhöhte Incidenz des HLA B27 ($P = 0{,}017$). In den Gruppen der paranoiden ($P = 0{,}005$), der chronisch Schizophrenen ($P < 0{,}001$) sowie bei Patienten mit ungünstiger Prognose ($P < 0{,}001$) und Patienten mit Krankheitsbeginn vor dem 20. Lebensjahr fand sich B27 mit erhöhter Incidenz. In den letzteren 3 Gruppen fand sich auch eine erhöhte Incidenz des HLA A9.

Die Kombination A9-B27 wurde in 0,63% der Kontrollgruppe und in 7% des Patientenkollektivs gefunden ($P < 0{,}001$). 85,7% der Träger dieser Kombination waren chronisch paranoid Kranke mit ungünstiger Prognose.

Diese Studie weist auf die Möglichkeit hin, daß die HLA-Bestimmung für genetische Studien, aber auch zur Differentialdiagnose und zur Prognose der Schizophrenie einmal von Nutzen sein könnte.

Schlüsselwörter: Schizophrenie – HLA-Antigene – Psychiatrische Genetik – Arthropathie

Introduction

The production of human leucocyte antigens (HLA) is controlled by a gene complex which is localized on chromosome 6. These HLA are very important in organ transplantation for they provide the best possible histocompatibility conditions. Various diseases with a noticeable autoimmune component and frequent occurrence within the family show a statistically significant correlation with specific HLA (for overview: Svejgaard et al., 1975).

This correlation was also shown in studies of HLA in some psychiatric disorders, namely the endogenous psychoses. Nevertheless, results have been contradictory. In eight studies of HLA in manic-depressive patients, 17 antigens were recognized which occurred with a different frequency in patients when compared with controls (16 of these antigens showed statistically significant differences). In nine investigations of HLA in schizophrenic patients, 28 antigens showed a different frequency in patients when compared with controls (23 of these antigens showed statistically significant differences).

Contrasted to studies in manic-depressive patients, HLA studies in schizophrenic patients showed a relatively greater homogeneity: HLA A1 appeared with an increased incidence in patients in six of nine studies, an increased frequency of HLA A9 was found in five of nine investigations, and HLA B27 frequency was decreased in three studies. Nevertheless, contradictory results also were found. HLA A10 frequency was decreased in three studies and increased in the fourth. HLA B17 appeared with a higher incidence in two works and a lower one in the results of another author (for overview: Gattaz and Beckmann, in press).

Various circumstances could explain the heterogeneity of the published results: the investigation of ethnically heterogeneous populations, the use of different diagnostic criteria, or the comparison of diagnostic groups of in-

adequate size. The purpose of this investigation was to study the HLA system in a homogeneous German population under administration of strict diagnostic criteria for schizophrenia.

Material and Methods

HLA A, B, and C loci were typed in 100 patients consecutively admitted into the Zentralinstitut für Seelische Gesundheit—Mannheim meeting research criteria for diagnosis of schizophrenia (Feighner et al., 1972). Only patients from the German population were included in the study to avoid influence deriving from different HLA distribution among races.

Histocompatibility antigen-typing was performed using standard lymphocytotoxicity microtest (Terasaki and McGlelland, 1964), and results were compared with a control group of 472 healthy individuals of the same ethnic origin. Patients and controls were typed in the same period of time with the same antisera in the immunological laboratory of the Städtische Krankenanstalten Mannheim (R. W. Ewald).

There were 56 female and 44 male patients. Ages ranged between 18 and 65 years (average 34.3 years). Applying diagnostic criteria from Spitzer et al. (1976), patients were subdivided in: (a) 61 paranoid and 19 hebephrenic and (b) 33 acute and 61 chronic schizophrenics. The disease onset in 31 patients was before the age of 20 and in 32 patients, after the age of 30. Using the prognostic criteria of Robins and Guze (1970), 29 patients were considered as having good prognoses and 58 as having poor prognoses. The subdivision of the patients was done without knowledge of HLA typing and vice versa (double-blind study).

The differences were tested with the chi-square test (Yates' correction) at a significance level of 0.05. Since differences for 31 antigens had to be tested, the problem of multiple statistical tests arose (at least one significant result is to be expected by chance with a level of 0.05). A way out of this difficulty is to multiply the p values obtained by the number of antigens (Bonferroni inequality). Whenever this value ($p \times 31$) remains below the level of significance assumed, the outcome is significant and is adjusted for the number of possibilities.

Results

The antigene frequency is shown in Table 1. In schizophrenic patients as a whole there was an increased incidence of HLA B27 ($P = 0.017$). The schizophrenic population was subdivided according to clinical and prognostic features and to the age of disease onset. HLA B27 appeared with an increased incidence in the subgroups of paranoid patients ($P = 0.005$), chronic schizophrenics ($P < 0.001$) patients with poor prognosis ($P < 0.001$), and in patients with onset of the disease before the age of 20 years ($P = 0.004$).

HLA A9 appeared with an increased incidence (not significant) in the total patient group and was found to be significantly increased in the subgroups of chronic schizophrenics ($P = 0.028$), patients with poor prognosis ($P = 0.045$), and in the subgroup of patients with disease's onset before the age of 20 years ($P = 0.038$). HLA Cw2 occurred with a decreased incidence in the subgroup of chronic patients ($P = 0.04$). The combination A9-B27 was found in 0.63% of our control group and in 7% of the patients ($P < 0.001$). Of these patients 85.7% were chronic paranoid patients with poor prognostic features.

To estimate the degree of association between our findings and schizophrenia we calculated the relative risk, as suggested by Woolf (1955). The relative risk indicates how many times more frequent the disease occurs in individuals

Table 1. HLA incidence in 100 schizophrenic patients and 472 healthy controls. Nosological differentiation according to research diagnostic criteria (Spitzer et al., 1976) and prognostic criteria (Robins and Guze, 1970)

HLA	Schizophrenia ($n = 100$)	Paranoid ($n = 61$)	Hebephrenic ($n = 19$)	Acute ($n = 35$)	Chronic ($n = 61$)	Good prognosis ($n = 29$)	Poor prognosis ($n = 58$)	Before 20 ($n = 31$)	After 30 ($n = 32$)	Control ($n = 472$)
1. Sublocus										
A1	25	22.9	21.0	31.4	18.0	31.0	17.2	16.1	31.2	26.9
A2	41	42.6	36.8	45.7	40.9	41.3	39.6	32.2	46.8	47.0
A3	31	34.4	26.3	31.4	29.5	34.4	34.4	41.9	18.7	27.1
A9	30	31.1	26.3	22.8	34.4	24.1	32.7	38.7	31.2	20.9
A10	11	13.1	15.7	17.1	8.1	13.7	8.6	6.4	15.6	16.3
A11	15	11.4	21.0	17.1	14.7	10.3	15.5	12.9	12.5	11.0
A28	9	3.2	15.7	5.7	11.4	6.8	10.3	12.9	9.3	10.3
A29	3	1.6	5.2	0.0	4.9	0.0	5.1	6.4	0.0	3.8
Aw30	2	1.6	5.2	0.0	3.2	0.0	3.4	0.0	0.0	4.0
Aw31	5	4.9	0.0	2.8	6.5	6.0	5.1	9.6	3.1	3.8
Aw32	5	8.1	5.2	8.5	3.2	10.3	3.4	0.0	12.5	6.7
2. Sublocus										
B5	11	11.4	21.0	8.5	13.1	3.4	15.5	22.5	6.2	13.1
B7	25	26.2	26.3	25.7	22.9	20.6	27.5	29.0	25.0	20.5
B8	15	11.4	10.5	11.4	14.7	10.3	13.7	12.9	18.7	13.9
B12	22	19.6	15.7	31.4	18.0	27.5	20.6	25.8	18.7	20.5
B13	2	1.6	0.0	2.8	1.6	0.0	3.4	0.0	3.1	5.7
B14	4	1.6	5.2	5.7	3.2	6.8	3.4	0.0	3.1	4.8
B15	13	16.3	10.5	8.5	13.1	13.7	13.7	12.9	21.8	13.3
Bw16	7	8.1	15.7	14.2	6.5	17.2	5.1	12.9	6.2	10.3
B17	11	13.1	10.5	11.4	11.4	13.7	8.6	6.4	12.5	7.2

B18	10	9.8	15.7	11.4	11.4	3.4	15.5	12.9	6.2	8.6
Bw21	4	4.9	0.0	2.8	4.9	3.4	1.7	0.0	12.5	6.7
Bw22	6	4.9	0.0	11.4	3.2	13.7	0.0	0.0	6.2	7.4
B27	16	19.6	10.5	5.7	22.9	6.8	22.4	22.5	6.2	7.8
Bw35	23	18.0	31.5	22.8	21.3	31.0	20.6	16.1	25.0	24.3
B40	13	16.3	5.2	14.2	13.1	13.7	10.3	6.4	15.6	15.4
3. Sublocus										
Cw1	8	9.8	5.2	11.4	6.5	13.7	5.1	6.4	3.1	5.0
Cw2	12	13.1	5.2	5.7	16.3	3.4	13.7	22.5	6.2	7.6
Cw3	23	29.5	15.7	25.7	19.6	27.5	18.9	16.1	28.1	22.4
Cw4	25	19.6	36.8	28.5	21.3	31.0	25.8	22.5	25.0	24.3
Cw5	2	1.6	0.0	2.8	1.6	3.4	1.7	6.4	0.0	2.7

carrying the antigen as compared to individuals carrying HLA A9 is 1.6; to HLA B27 it is 2.2; and to individuals carrying the combination A9-B27, 11.7.

After P values were corrected for the number of antigens (Bonferroni inequality), the association with HLA B27 in the subgroups 'chronic patients' and 'patients with poor prognosis' remained significant, as did the association with the combination A9-B27 in the total patient group.

Discussion

Our findings give support to the hypothesis that the term schizophrenia is used to designate a group of genetically heterogeneous diseases. When comparing the total patient group with controls, we found a positive association with HLA B27. Although this association was significant, it did not resist the P value correction. Nevertheless, when the total patient group was subdivided into more homogeneous subgroups, the associations became stronger in the subgroups of patients which satisfied the Kraepelinian concept of schizophrenia (early onset, poor prognosis, and chronicity). In fact, when we classified a subgroup of 25 patients presenting all three features, we found the strongest associations to HLA A9 and B27. The first appeared in 56% of the patients as compared with 20.9% in controls ($P < 0.001$) and the latter in 36% of patients as compared with 7.8% in controls ($P < 0.0005$).

On the other hand, the incidence of HLA in the subgroups of patients with acute schizophrenia, late disease onset, and good prognosis did not present any significant difference to the control group. This fact obscured the associations with HLA B27 and mainly with A9 when the total heterogeneous schizophrenic group was considered, and it could explain why some authors failed to find significant associations between HLA and schizophrenia.

Comparing our results with those from other authors, we observe that the increased incidence of HLA A9 appeared in five other studies (Cazzullo et al., 1974; Eberhard et al., 1975; Smeraldi et al., 1976; Julien et al., 1977 and 1978; Crowe et al., 1979); HLA B27 which occurred with an increased incidence in our patients was found decreased in three other studies (Cazzullo et al., 1974; Smeraldi et al., 1976; Julien et al., 1977 and 1978). It is worth noting that HLA B27 has a strong association with some arthropathies (e.g., ankylosing spondylitis, with a relative risk of about 120). However, since 1936 a great number of reports indicate that schizophrenic patients suffer very seldom from arthropathy, when compared with the nonschizophrenic population (for overview: Österberg, 1978), and the few schizophrenic patients with arthropathy suffered from an atypical psychosis (e.g., schizo-affective psychosis). *None of our 16 patients with HLA B27 (and none of our 100 patients) had an atypical psychosis and nine of them suffered from schizophrenia according to the classical Kraepelinian definition.* Although, none of these 16 schizophrenics with HLA B27 have a diagnosis of arthropathy, most of them are still in a younger age to onset of this disease. Therefore, the question of whether arthropathy and chronic paranoid schizophrenia are mutually exclusive remains a matter of ongoing research.

This study supports the possibility of using HLA typing in genetic studies of schizophrenia as well as in differential diagnosis and prognosis. However, in view

of the large number of antigens and the relatively small number of patients studied, further research based on solid methodological procedures would be necessary to clarify the association between HLA and schizophrenia.

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