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Family Studies in Multiple Sclerosis: HLA Haplotypes of Affected Sib-Pairs

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Summary. The occurrence of multiple sclerosis (MS) in several members of families has been observed in 4.8% of 105 MS patients from a limited epidemiological area of Rostock. Typing of the HLA antigens in 4 affected sib-pairs showed two identical HLA haplotypes in 3 of the pairs: 1 pair shared one haplotype. These findings point to a dominant mode of inheritance of the disease susceptibility gene together with the HLA haplotype. The assessment of family studies in MS is discussed.

Key words: Multiple sclerosis - Histocompatibility (HLA) haplotypes - Sib-pairs - Family studies

Zusammenfassung. In einem umschriebenen epidemiologischen Rostocker Areal wurde bei 105 Patienten mit einer MS zu 4,8% das Auftreten der Erkrankung bei mehreren Familienmitgliedern beobachtet. Die Bestimmung der HLA-Antigene bei vier erkrankten Geschwisterpaaren erbrachte für drei der MS-Paare zwei und für ein Paar einen identen HLA-Haplotyp. Die Ergebnisse deuten auf einen dominanten Erbgang des mit dem HLA-Haplotyp vererbbaren Prädispositions-Gens. Die Wertigkeit und Grenzen der Familienstudien bei der MS werden erörtert.

Schlüsselwörter: Multiple Sklerose - Histokompatibilitäts (HLA)-Haplotypen - Geschwisterpaare - Familienuntersuchungen

Introduction

The appearance of multiple sclerosis (MS) in more than one member of a family has been observed in between 2.6% and 12% of cases [8]. Therefore a 5-20 times more frequent risk in affected families is found: it is especially high (30-40 times) among siblings. Family analyses in HLA-associated diseases are carried out presuming a disease susceptibility gene within the region of HLA [2]. The supposed MS-susceptibility gene (MSSG) is inherited in linkage with the HLA haplotype, whereby the HLA haplotype acts as a "marker" [11].

The present study reports on the familial occurrence of MS, especially the distribution of HLA haplotypes in affected siblings. For observing the mode of inheritance of the MSSG in the sib-pair double-case, those families with at least one MS-affected sib-pair have been taken into account. The comparison of haplotypes between healthy and affected siblings has not been undertaken because of the following disadvantages: (a) up to 20% of cases of MS may be clinically silent, so that affected members are not detectable [4] and (b) "healthy" members may be affected in their lifespan [16].

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Patients and Methods

Of 105 MS patients from the urban and rural district of Rostock 4 MS-affected sib-pairs were HLA-typed. The definition of MS cases was according to the criteria stated [7] (including the parameters of CSF): 56 patients showed a relapsing-remittent and 49 a chronic progressive course; 65 patients displayed slight to moderate dynamics (i.e. progression of the disease) and 40 middle severe to severe. Additionally the HLA-antigens of ten families with one MS member were determined.

The HLA-A,B,C-typing was performed in the microlymphocytotoxicity test (LCT) as previously described [14]. B-lymphocytes for HLA-DR-typing were isolated by the "Nylon-Wool-Method" and tested in the modified LCT [6]. We used a panel of typing sera of the GDR (HLA-serumset I of the HFR Organ- und Gewebetransplantation der DDR) and additionally 80 test sera partly from other reference laboratories [14]. The statistical analyses were carried out as mentioned previously [13].

Results and Discussion

The occurrence of MS in several members of a family was observed in 4.8% of our patients. They concerned 4 sib-pair double-cases and 1 affected mother and daughter. Of the 4 affected sib-pairs 3 shared two identical HLA haplotypes and 1 pair shared one (Table 1). In this respect the supposed MSSG was marked in each family with one HLA haplotype. The present investigations show a ratio of $4:4=1.0$ between the observed and the expected MS pairs with at least one identical haplotype. From this a dominant mode of inheritance of the MSSG may be supposed.

Analogous family data and hints at a dominant action of the HLA-linked MSSG with low penetrance have been recorded by Tiwari et al. [11, 12] and Zander et al. [16]. The latter observed among 34 MS-affected sib-pairs a total of 28 pairs with at least one identical haplotype and only 6 pairs without such sharing (presenting a ratio of $28:34=0.82$). In 4 families with 2 MS members in each case Olsson et al. [9] could not find any affected pair without an identical haplotype. Exceptions of the expected segregation of MS with the HLA haplotype (i.e. deviations from 1.0) may be explained by a recombination be-

Table 1. HLA haplotypes of sib-pair double-cases with MS

Sib-pairs	Sex/Age	HLA haplotypes	Number of identical haplotypes
B., E.	F/44	HLA-A2,B7,DR2/A28,B15,Cw3,DR4	2
B., L.	F/54	A2,B7,DR2/A28,B15,Cw3,DR4	
N., M.	F/31	HLA-A1,B8,DR3/Aw32,Bw35,DR2	2
R., G.	F/37	A1,B8,DR3/Aw32,Bw35,DR2	
G., G.	F/39	HLA-A28,B14,DRw6/A3,B12,DR7	2
S., H.	F/40	A28,B14,DRw6/A3,B12,DR7	
W., L.	F/50	HLA-A2,Bw35,Cw4,DR3/A26,B27,DR5	1
W., S.	M/42	A2,Bw35,Cw4,DR3/A2,B15,DR3	

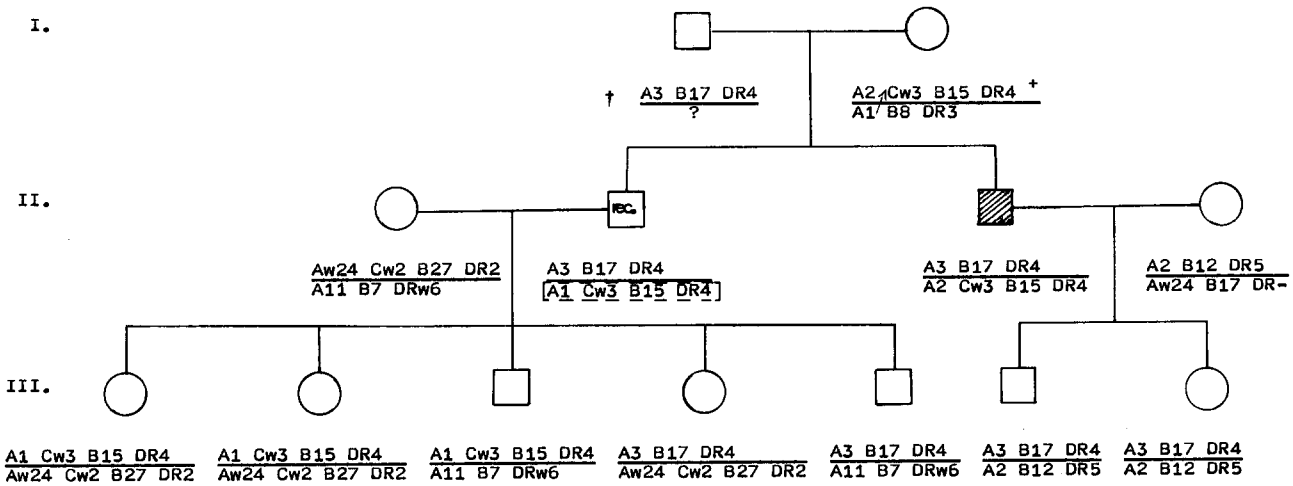

Fig. 1. Recombination between the HLA-A and C-loci in a MS-family (○=female, □=male relative; ▨=MS-patient; ↗=crossing over; +=haplotype constellation of the patient's mother assumed from the Caucasian HLA haplotype frequencies (14), in this constellation the recombination would be in the healthy brother; rec.=recombination; □=recombinant haplotype)

tween the HLA loci and the MSSG. Recombinations within the HLA system are detectable regarding the HLA pattern, and have to be excluded in family analyses.

In our supplementary studies of 10 families a recombination in 1 case (Fig. 1) has been observed. It was caused by a crossing over between the HLA-A and C-loci of the mother. We could define only her HLA phenotype: From the Caucasian haplotype frequencies [14] the haplotypes A1, B8/A2, Cw3, B15 may be assumed for the mother; so the recombination refers to the MS-patient's healthy brother. Due to the A/C-crossing over of the mother the sons were different in their A locus antigens. The region of the chromosome 6 bearing the HLA-DR-locus was not altered by the crossing over and identical in both the brothers. As the presumed MSSG is supposed to be near the HLA-DR-locus [11, 12] it is not influenced by the crossing over between the A and C-locus. It may be concluded that both the brothers have the same genetic factors in the HLA-DR and in the DS-region. The fact that only one was affected can be explained by the complexity of the etiology of MS (environmental, viral and endogenic factors) [13]—or by the arguments mentioned in the introduction.

In a summarizing study Alter and Quevedo [1] referred to the difficulties in segregation analyses of MS and HLA haplotypes with regard to affected and healthy members of a family. They concern the facts mentioned above and crossing over within the HLA system, the family size (including the incomplete typing), the age and the different degrees of relationship between the affected members, which may yield negative results, i.e. non-attendance of segregation of MS and HLA haplotypes. In this respect the statements received from analyses of HLA haplotypes in members of MS families are restricted [3, 5, 10]. Among monozygotic twins, too, a discordance in MS may be observed; however, in some cases the CSF findings (CSF-Ig) suggest the possibility of a subclinical course of MS [15]. On the other side, in the sib-pair double-case approach the joint segregation of MS with at least one HLA haplotype may be demonstrated [16].

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