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Juvenile myoclonic epilepsy and human leukocyte antigens

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The idiopathic generalized epilepsies (IGE) occur with a high aggregation within families. Juvenile myoclonic epilepsy (JME) is recognized as a commonly occurring form of idiopathic generalized epilepsy. A possible association between JME and HLA antigens was investigated by serological typing of human leukocyte antigens (HLA) class I antigens and by DNA oligotyping of class II antigens. Twenty-four patients and 129 controls, all Caucasians of Scandinavian descent, were tested. Uncorrected there was a significant positive association (Relative risk (RR) = 8.07) to B17 and a significant negative association (RR = 0.13) to B8 as well as DRB1*3. The negative association to DQ alleles DQA1*0501 and DQB1*0201, which are in strong linkage disequilibrium with the alleles B8 and DRB1*3, was weaker and not significant, thus giving no clue as to a primary HLA-DQ association of JME.

Key words: epilepsy; juvenile myoclonic epilepsy; genetics; HLA antigens; disease susceptibility.

INTRODUCTION

The epilepsies are divided into two major classes: the generalized and the localization-related epilepsy syndromes. Both are separated into idiopathic (no other underlying cause than a presumed genetic predisposition), symptomatic (known aetiology), and cryptogenic (unknown aetiology, but presumably symptomatic)[1].

Juvenile myoclonic epilepsy (JME) is a common idiopathic generalized epilepsy syndrome, which, clinically, is easily identified. It occurs in 5–10% of patients with epilepsy. The characteristic myoclonic jerks predominantly occur after premature awakening. Most patients have generalized tonic–clonic seizures (GTCs), and up to one third have typical absence seizures[2].

Many investigations have been performed in search of an HLA association in epilepsy. Some patient series have been mixtures of different syndromes, and the results may seem confusing. Previously, mainly HLA class I antigen associations were studied as reviewed by Eeg-Olofsson *et al*[3]. Lately, the interest has focused on JME. Possible associations to HLA class I antigens[4] as well as class II (DR)[5] have been reported.

The first linkage study was reported by Delgado-Esqueta *et al*[4] in JME and concluded with a lod score over 3.0 for a localization of the disease gene to the HLA region (chromosome 6p21.3) and dominant inheritance with a penetrance of 0.9 as the most probable mode of inheritance. JME and its associated EEG trait had been ascribed a genetic predisposition, and the HLA region on the short arm of chromosome 6 thus became involved as the tentative location of a disease gene. The linkage studies of Delgado-Esqueta *et al* have since mainly been confirmed by two studies[6,7]. Recent investigations have, however, provided evidence against linkage between JME and the HLA region in some pedigrees[8,9,10] suggesting heterogeneity within the syndrome of JME.

The aim of the present study was to re-evaluate a possible HLA association of JME, especially regarding the class II antigens, as DNA oligotyping now gives a much better discrimination between alleles than the former serotyping, and because this class of antigens, especially the DQ series, have been drawn into focus of interest as the most probable predisposing HLA genes in an increasing number of diseases[11].

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SUBJECTS AND METHODS

Twenty-four consecutive outpatients with JME were examined. They were 13 females and 11 males with an age range from 13 to 64 years (mean, 28 years). Epilepsy onset age ranged from 8 to 19 years (mean, 15 years). All patients had experienced myoclonic jerks with morning predominance; 22 had suffered from GTCs, and five presented a history of absence seizures, three with atonic components.

Table 1: Distribution of HLA alleles among juvenile myoclonic epilepsy patients and controls

HLA alleles	JME patients $n = 24$ no. (%)	Controls $n = 129$ no. (%)	P†	RR
DQA1*0101	5 (20.8)	31 (24.0)	ns	0.83
DQA1*0102	11 (45.8)	55 (42.6)	ns	1.14
DQA1*0103	4 (16.7)	22 (17.1)	ns	0.97
DQA1*0201	6 (25.0)	22 (17.1)	ns	1.62
DQA1*030X§	10 (41.7)	55 (42.6)	ns	0.96
DQA1*0401	3 (12.5)	11 (8.5)	ns	1.53
DQA1*0501‖	3 (12.5)	37 (28.7)	ns	0.36
DQA1*0601	0 (0.0)	1 (0.8)	ns	1.75
DQB1*0501	4 (16.7)	28 (21.7)	ns	0.72
DQB1*0502	0 (0.0)	1 (0.8)	ns	1.75
DQB1*05031	2 (8.3)	3 (2.3)	ns	3.82
DQB1*05032	0 (0.0)	0 (0.0)	—	—
DQB1*0601	0 (0.0)	0 (0.0)	—	—
DQB1*0602	6 (25.0)	36 (27.9)	ns	0.86
DQB1*0603	4 (16.7)	23 (17.8)	ns	0.92
DQB1*0604,5	4 (16.7)	24 (18.6)	ns	0.88
DQB1*0201	4 (16.7)	47 (36.4)	ns	0.35
DQB1*0301	6 (25.0)	23 (17.8)	ns	1.54
DQB1*0302	8 (33.3)	34 (26.4)	ns	1.40
DQB1*0303X	2 (8.3)	14 (10.9)	ns	0.75
DQB1*0401	0 (0.0)	0 (0.0)	—	—
DQB1*0402	3 (12.5)	13 (10.1)	ns	1.27
DRB1*1‡	4 (16.7)	24 (18.6)	ns	0.88
DRB1*2	8 (33.3)	37 (28.7)	ns	1.24
DRB1*3	1 (4.2)	33 (25.6)	0.04	0.13
DRB1*4	10 (41.7)	46 (35.7)	ns	1.29
DRB1*5	2 (8.3)	7 (5.4)	ns	1.13
DRB1*6	10 (41.7)	50 (38.8)	ns	1.13
DRB1*7	6 (25.0)	22 (17.1)	ns	1.72
DRB1*8	3 (12.5)	14 (10.9)	ns	1.17
DRB1*9	0 (0.0)	9 (7.0)	ns	0.26
DRB1*10	1 (4.2)	4 (3.1)	ns	1.36
	$n = 124$			
A1	6 (25.0)	33 (26.6)	ns	0.92
B8	1 (4.2)	32 (25.8)	0.04	0.13
B17	4 (16.7)	3 (2.4)	0.01	8.07

† P-values are not corrected.
‡ The broad DRB1 specificities are denoted DRB1*1 to DRB1*10.
§ X denotes all sub-alleles described.
‖ Three sub-alleles of DQA1*0501 are described recently[12]. For convenience the denotion DQA1*0501 is used for these sub-alleles.

The control group consisted of 129 persons, randomly selected members of the hospital staff and blood donors. Patients and controls were all Caucasians of Scandinavian descent and all living in the same geographical area of Mid-Norway.

INVESTIGATIONS

The PCR amplification and SSO probing of HLA DR and DQ were performed as previously described[12]. The nomenclature for the HLA alleles and the specificities of the SSO probes are in accordance with a recently-published gene registry of HLA class II nucleotide sequences[13], excepting the broad specificities of DRB1. These are denoted as follows: DRB1*01,DRB1*15,16, DRB1*03, DRB1*04, DRB1*11,12, DRB1*13,14 DRB1*07,DRB1*08, DRB1*09 and DRB1*10. These DRB1 designations correspond to the more widely known serological DR nomenclature.

Serological HLA typing was performed as described by Vartdal and co-workers[14].

The chi-square test with Yates' correction was used to compare the number of patients and controls positive for an allele or a haplotype. The level of significance was set to 0.05. Relative risk (RR) was calculated by Woolf's formula, with Haldane's modification in sets containing zero[15].

RESULTS

The results of the HLA typings are shown in Table 1. The frequencies of all the DNA-typed class II alleles are presented. The distribution of class II antigens among controls are quite similar to what has been published for another Norwegian population[16]. Only the class I antigens significantly deviating from the controls or of special interest are included. The *P* values presented have not been corrected for number of antigens tested.

We found a statistically significant positive association between JME and the HLA antigen B17 and a significant negative association between JME and the antigens B8 and DRB1*3. We found no clue for a stronger association to the DQ series of class II alleles than to class I or to DRB1 alleles.

DISCUSSION

A great number of HLA associated diseases have been reported throughout the last decades, most

of which have a dysregulated immune system and autoimmunity as predominant features. (For review see Tiwari and Terasaki[17].) Such associations are now generally supposed to be primarily to alleles of the HLA molecules proper and to depend on the different peptide binding properties which these alleles have when presenting autoantigens and exogenous antigens to the immune-regulating T-lymphocytes[18]. Other diseases are HLA associated merely because the predisposing gene happens to be located in the HLA region without any overt involvement of the immune system. The results of this kind of investigation are, for some diseases, much dependent on the ethnic background and homogeneity of the population studied.

The results of clinical family studies have shown that the different forms of idiopathic, generalized epilepsies may share a common genetic factor[4]. In addition, there is a tendency towards a familial aggregation of the more specific syndromes, such as childhood and juvenile absence epilepsies, JME, and epilepsy with GTCs on awakening. Some degree of overlap between the forms during the clinical course seems to occur, and it has been suggested that a defect on chromosome 6p predisposes to the idiopathic generalized epilepsies in general[19].

An association between epilepsy in children and HLA-B17 has been reported by Serclova *et al*[20]. Their patients seemed to suffer from various seizure types, predominantly belonging to the localization-related form of epilepsy. None of the children seemed to have JME. The relevance of the B17 association that we detected in JME thus needs to be confirmed.

The HLA antigens A1; B8, DR3 (DRB1*3) together with the DQ alleles DQA1*0501 and DQB1*0201 are in strong linkage disequilibrium (occur together on the same chromosome more often than expected) and represent the most frequent extended HLA haplotype in the Caucasian and especially northern European population[16,21,22]. Our finding of a negative association between JME and the HLA haplotype carrying B8, DRB1*3 has not been reported previously. Eeg-Olofsson *et al*[23] have, however, reported a negative association between HLA-A1, B8 and a study mainly consisting of children with benign epilepsy of childhood and absences. They did not determine the class II antigens. In our study the negative association does not include A1, whereas it does include DRB1*3 and the DQ-alleles DQA1*0501 and DQB1*0201. The negative DQ associations are not statistically significant, however. The negative association that we detected for HLA-B8, DRB1*3 in JME contrasts to the positive association reported for HLA-A1, B8 by Fichsel and Kessler[24] as well as by Rivas[25] in absence epilepsy. For HLA-B8 our result gives a chi-square of 10.5 versus the result of Fichsel and Kessler which may accentuate the probability that JME and absence epilepsy are indeed genetically different.

The possible HLA associations previously reported in JME: B18 (negative), B52, B62[5], and DRw6[4] were not detected in our series, i.e. we were typing for B5 and B15 which are including B52 and B62, respectively.

Also in the localization-related epilepsies some degree of heredity may be present[26,27]. We have HLA-typed a study of 20 patients suffering from localization-related epilepsy with complex partial seizures, no cerebral MR abnormalities, and with cryptogenic cause, without detecting any HLA association (unpublished).

The total picture of a possible genetic relationship between epilepsy and the HLA region is rather bewildering, and it is difficult to reach a decisive conclusion that such a relationship exists at all. If epilepsy syndromes are HLA-associated, the different HLA associations reported probably favour the idea of an association that is primarily not to the class I or II antigens, and the disease is also not of an overt autoimmune character, even if a dysregulation of T-lymphocytes in JME patients has been described[28]. HLA associations of typical autoimmune diseases mainly tend to extend across ethnic and even racial borders. Of the HLA associated diseases of the central nervous system, multiple sclerosis has a clearly autoimmune pathogenesis that is mainly genetically determined[29], whereas in narcolepsy, the disease exhibiting the strongest HLA association detected so far, autoimmunity is not an evident characteristic[30].

Of 58 HLA alleles studied in JME we detected the same positive association as Serclova *et al*[20] and partly the same negative association as Eeg-Olofsson *et al*[23] did in other epileptic syndromes. The question of whether this is incidental or indicates a common genetic aetiologic factor, needs further investigation. Genetic linkage studies can be performed on whichever family with two or more occurrences of a disease irrespective of ethnic background, and will also give information on a possible genetic relationship between for instance different IGE syndromes. It should be stressed, however, that HLA association studies must be performed on clinically as well as ethnically homogenous

patient series. If these issues are going to be settled, it is important that investigations performed are comparable if not sufficiently comprehensive to be conclusive alone.

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