The Significance of HLA DRB1*1501 and Oligoclonal Bands in Multiple Sclerosis: Clinical Features and Disability

Renata Balnytė[1], Daiva Rastenytė[1], Ingrida Ulozienė[2], Dalia Mickevičienė[1], Erika Skrodenienė[3], Astra Vitkauskienė[3]

[1]Department of Neurology, Medical Academy, Lithuanian University of Health Sciences,
[2]Department of Ear, Nose, and Throat Diseases, Medical Academy, Lithuanian University of Health Sciences,
[3]Department of Laboratory Medicine, Medical Academy, Lithuanian University of Health Sciences, Lithuania

Key words: *multiple sclerosis; human leukocyte antigen DRB1*1501; oligoclonal bands; clinical features; disability.*

Summary. *The aim of the present study was to determine the value of immunogenetic risk factors and to estimate their relationship with the clinical features and disability status of patients with multiple sclerosis in a Lithuanian population.*

Materials and Methods. This was a prospective study of 80 patients with multiple sclerosis. The diagnosis of multiple sclerosis was based on the revised McDonald criteria. Oligoclonal bands (OCBs) of immunoglobulin G (IgG) were tested using isoelectric focusing and IgG specific immunofixation. HLA DRB1 alleles were genotyped using polymerase chain reaction.

*Results. Of all patients, 55% were positive for OCBs and 56% for HLA DRB1*1501. OCB-positive patients with multiple sclerosis had higher EDSS scores than their OCB-negative counterparts at onset of the disease (3.93±1.21 and 3.36±0.96 points, respectively; P=0.02) and during the last visit (4.31±2.06 and 3.09±1.98 points, respectively; P=0.009). The mean relapse rate was higher in the OCB-positive group compared with OCB-negative group (1.45±0.69 and 0.58±0.64, respectively; P=0.001). OCB-positive patients had higher IgG index compared with OCB-negative patients (P=0.0001). No relationship was found between HLA DRB1*1501 antigen status and the clinical features or EDSS score, and presence or absence of OCB in the present subset of patients with multiple sclerosis.*

*Conclusions. The presence of oligoclonal bands in the cerebrospinal fluid of the patients with multiple sclerosis was associated with the greater number of exacerbations, higher degree of disability, and higher IgG index. There were no significant associations between the presence of HLA DRB1*1501 allele and the clinical symptoms, course of disease, or disability score.*

Introduction

Multiple sclerosis (MS) is the most common and severe idiopathic demyelinating disease of the central nervous system with etiopathogenesis involving a complex interaction between genetic and environmental factors (1–4). Epidemiological data support a view that MS is caused or triggered by some environmental factors in persons who are genetically susceptible (4). Genes within the human leukocyte antigen (HLA) region account for the largest part of the genetic risk for MS as well as some other immunologically mediated diseases, such as diabetes, seronegative spondyloarthropathies, systemic lupus erythematosus, rheumatoid arthritis, etc. (5).

The strongest association signal comes from HLA-DRB1 in the class II region (4). A great variety of recently reported linkage and genome-wide association studies have established that the most important genetic risk factor in MS is carriage of a single copy of the HLA class II allele DRB1*15 to homozygote forms (6–8). About 60% of MS patients in Northern Europe are positive for HLA-DRB1*15, compared with 30% of healthy controls (9).

The HLA complex is not only associated with the disease development, but can also influence certain clinical features and immunological changes in the patients with MS. The interdependence of HLA-DRB1 genotype and phenotypic status of oligoclonal bands has been suggested (6). The higher prevalence of HLA-DRB1*1501 allele may be linked to an earlier onset of the disease, less favorable course, and female gender, the factors which are believed to be particularly important in the prognosis and treatment of MS (10, 11).

Oligoclonal bands (OCBs) of immunoglobulin G (IgG) are present in the cerebrospinal fluid (CSF) of the majority (85%–95%) of clinically definite MS patients and are believed to reflect the intrathecal synthesis of IgG antibodies (12, 13). Detection of the heightened intrathecal IgG synthesis or the pres-

Correspondence to R. Balnytė, Department of Neurology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50028 Kaunas, Lithuania. E-mail: rbalnyte@yahoo.com

Adresas susirašinėti: R. Balnytė, LSMU MA Neurologijos klinika, Eivenių 2, 50028 Kaunas. El. paštas: rbalnyte@yahoo.com

ence of OCBs was used in conjunction with clinical evidence to help satisfy the "dissemination in space" requirement of the previous Poser criteria and currently does the same for the revised diagnostic McDonald criteria, when magnetic resonance imaging (MRI) lesions alone do not suffice (14). The prognostic significance of OCBs as well as its association with the HLA-DRB1 genotype has been suggested by some studies but not confirmed by others (1, 6, 14, 15).

According to the World Health Organization, Lithuania belongs to the region with a high prevalence and incidence of MS (16). There is a lack of investigative studies, establishing the factors influencing disease appearance and its course, estimating the treatment options and prognostic information. To date, no studies have been carried out and no data have been published evaluating immunogenetic status in MS patients of Lithuanian origin. Therefore, the aim of this present study was to determine the value of immunogenetic risk factors and to estimate their relationship with the clinical features and disability status of MS patients in a Lithuanian population.

Material and Methods

Subjects. The study group comprised the patients with MS, older than 18 years, who were referred to the Department of Neurology at the Hospital of Lithuanian University of Health Sciences in Kaunas during 2009–2010 and who agreed to participate in the study. The study included only patients with confirmed MS diagnosis. MS diagnosis was made according to the widely accepted and revised McDonald criteria (2005) (17). All the laboratory data (OCB status), MRI findings, and data of visual evoked potentials (VEPs) were reviewed retrospectively from the medical records of the patients. Lumbar puncture and cerebrospinal fluid examination was performed at the time of diagnosis. All imaging studies were conducted with a 1.5-T MR scanner (MAGNETOM Avanto, Siemens, Erlangen, Germany) with a standard head coil. The institutional MRI protocol for patients with suspected MS consisted of the following: 1) transverse or sagittal T2-weighted turbo spin-echo sequences (repetition time/echo time/ flip angle, 2.800/13/150); 2) transverse or sagittal T2-FLAIR sequences (9.000/89/2/TI 2.500); and 3) transverse T1-weighted spin-echo sequences (608/17/90) before and after administration of gadolinium IV (10 mL/50 kg). The standard pattern-shift VEPs were recorded for all 80 patients. Registration of VEPs was done by the Evoked Potential Navigating System (Bio-Logic System Corp., USA). The responses were considered abnormal if the P100 latency was longer than 114 ms (i.e., 2 SD above the mean) (18).

Demographic (age at onset of the first symptoms, gender) and clinical data (disease course, duration of the symptoms, disability status) and the findings of all paraclinical tests were collected for all patients. Disability was measured using the Kurtzke Expanded Disability Status Scale (EDSS). The patients were followed up prospectively, and their clinical status was checked every three months.

OCB Testing and HLA Genotyping. Matched CSF and plasma samples were analyzed using isoelectric focusing and IgG specific immunofixation to test the presence of intrathecal specific oligoclonal banding and compared directly with the serum samples (14). Positive oligoclonal banding was defined as more than 2 bands present in the CSF, but absent in the corresponding blood serum (19). The IgG index was calculated from the serum and CSF albumin and IgG concentrations using the following formula:

IgG index = (CSF IgG / serum IgG) / (CSF albumin / serum albumin).

The IgG index was considered as high if it was $\geqslant$0.70 (14).

Blood samples were obtained from patients with MS and stored at –20°C. DNA was extracted from blood leukocytes by the standard phenol-chloroform method. DNA was dissolved in the sterile double distilled water. HLA DRB1 alleles for patients with MS were genotyped using the polymerase chain reaction (PCR) with amplification of the second exon of the genes. An amplified product was manually dot blotted onto nylon membranes. Synthetic sequence-specific oligonucleotide probes were 3′-end-labeled with αP32-dCTP and used for hybridization followed by stringency washes and autoradiography. HLA DRB1 alleles were genotyped using the PCR with sequence-specific primers (HLA DRB1*15/16- PCR, PROTRANS Medicinische Diagnostische Produkte GmbH, Germany) and following the manufacture's recommendations. The amplified products were determined by means of agarose gel electrophoresis (20). Laboratory analyses were carried out at the Laboratory of Clinical Chemistry and Genetics, Hospital of Lithuanian University of Health Sciences.

The study was approved by the Kaunas Regional Bioethics Committee. Informed consent form was signed by each patient before the entering the study.

Statistical Analysis. Analysis of the collected data was performed using the statistical package SPSS version 13.0. Clinical variables (disease duration, EDSS score, relapse rate) between groups with or without oligoclonal bands and HLA DRB1*1501 were analyzed with the nonparametric Mann-Whitney *U* rank test. Comparisons of mean ages

at onset across the groups were carried out using the Student *t* test. Parametric statistics were used for the normally distributed quantitative variables (estimated with the Kolmogorov-Smirnov and Shapiro-Wilk tests); and means with standard deviation (SD) were calculated. The χ^2 test was used to compare the qualitative variables and to estimate possible correlations. Odds ratios (OR) with 95% confidence interval (CI) were calculated to estimate associations. The significance level of α=0.05 and *P* values less than 0.05 ($P<\alpha$) were considered as statistically significant.

Results

Of the 80 patients with MS, two-thirds (67.5%) had the relapsing-remitting disease course. The mean duration of the symptoms was 10.1 years (SD, 6.74). The male-to-female ratio was 1:1.67. The disease most frequently manifested by visual symptoms (73.7%), followed by the brainstem (47.5%) and pyramidal symptoms (40.0%) (Table 1).

Of all the patients, 55% were positive for OCBs and 56% for HLA DRB1*1501. Immunogenetic risk factors and main clinical features of patients with MS by presence or absence of OCBs or HLA DRB1*1501 are presented in Table 2.

The EDSS scores were higher in OCB-positive than OCB-negative MS patients at diagnosis of the disease (3.93 and 3.36, respectively; *P*=0.02) and at the last visit (4.31 and 3.09, respectively; *P*=0.009). The elevated IgG index was found in 52.5% of the patients. OCB-positive patients had higher IgG index and mean relapse rate per year than OCB-negative patients (0.93 versus 0.53, *P*=0.001, and 1.45 versus 0.58 per year, *P*=0.001) (Table 2).

Table 1. The Main Demographic and Clinical Data of 80 Patients With Multiple Sclerosis

Characteristic	Value
Male-to-female ratio	1:1.67
Age at onset, mean (SD) [range], years	33.2 (8.87) [16–55]
Disease course:	
Relapsing-remitting	54 (67.5)
Secondary progressive	18 (22.5)
Primary progressive	8 (10.00)
Duration of the symptoms, mean (SD), years	10.1 (6.74)
Duration of the disease (time of diagnosis), mean (SD), years	6.66 (3.61)
Relapse rate per year, mean (SD)	1.06 (0.80)
First symptoms:	
Pyramidal	32 (40.0)
Sensory	30 (37.5)
Visual	59 (73.7)
Gastrointestinal/bladder	13 (16.2)
Cerebellar	27 (33.7)
Brainstem	38 (47.5)
Mental	14 (17.5)
EDSS score during the last visit, mean (SD)	3.76 (2.10)
EDSS score at the time of diagnosis, mean (SD)	3.67 (1.13)
Lesions on MRI:	
Periventricular	76 (95.0)
Corpus callosum	74 (92.5)
Brainstem	53 (66.3)
Cerebellum	41 (51.3)
Juxtacortical	35 (43.8)
Spinal cord	17 (21.3)
VEP abnormalities, OS/OD	54 (67.5)/60 (75)
IgG index, mean (SD)	0.75 (0.34)

Values are number (percentage) unless otherwise indicated. SD, standard deviation; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; VEP, visual evoked potential; IgG, immunoglobulin G; OS, oculi sinistri; OD, oculi dextra.

Table 2. Immunogenetic Risk Factors and Main Clinical Features in Patients Multiple Sclerosis by Presence or Absence of Oligoclonal Bands or HLA DRB1*1501

Factor	OCB-positive N=44	OCB-negative N=36	*P*	HLA DRB1*1501-positive N=45	HLA DRB1*1501-negative N=35	*P*
Male-to-female ratio	1:1.42	1:2.0	0.5	1:1.25	1:2.5	0.2
Age at onset, mean (SD), years	33.1 (9.27)	33.5 (8.47)	0.19	33.4 (9.02)	33.1 (8.79)	0.42
Relapse rate per year, mean (SD)	1.45 (0.69)	0.58 (0.64)	0.001	1.15 (0.85)	0.94 (0.72)	0.34
IgG index	0.93 (0.35)	0.53 (0.16)	0.0001	0.80 (0.36)	0.69 (0.31)	0.18
Positive for HLA DRB1*1501	27 (61.3)	18 (50.0)	0.3	–	–	–
EDSS score at the time of diagnosis, mean (SD)	3.93 (1.21)	3.36 (0.96)	0.02	3.74 (1.12)	3.59 (1.15)	0.5
EDSS score at last visit, mean (SD)	4.31 (2.06)	3.09 (1.98)	0.009	3.94 (2.15)	3.54 (2.04)	0.4
Disease course:						
RR	26 (59.1)	28 (77.8)		29 (64.4)	25 (71.4)	
SP	12 (27.3)	6 (16.7)	0.2	12 (26.7)	6 (17.2)	0.6
PP	6 (13.6)	2 (5.6)		4 (8.9)	4 (11.4)	
Relapsing-remitting course	26 (59.1)	28 (77.8)	0.076	29 (64.4)	25 (71.4)	0.5
Progressive course	18 (40.9)	8 (22.2)		16 (35.5)	10 (28.6)	

Values are number (percentage) unless otherwise indicated. OCB, oligoclonal band; RR, relapsing-remitting, SP, secondary progressive, PP, primary progressive, EDSS, Expanded Disability Status Scale.

Table 3. A Relationship Between the Lesions on Magnetic Resonance Images and the Immunogenetic Factors

Anatomical Location of Lesions on MRI*	OCB+ N=44	OCB– N=40	*P*	HLA+ N=45	HLA– N=35	*P*
Periventricular	40 (91.0)	36 (90.0)	0.063	44 (98.0)	32 (91.0)	0.2
Corpus callosum	40 (91.0)	34 (85.0)	0.5	41 (91.0)	32 (91.0)	0.6
Brainstem	35 (79.5)	18 (45.0)	0.005	34 (75.5)	19 (54.0)	0.0046
Cerebellar	26 (59.0)	15 (37.5)	0.1	26 (58.0)	15 (43.0)	0.2
Juxtacortical	25 (56.8)	10 (25.0)	0.009	20 (44.0)	15 (43.0)	0.9
Spinal cord	11 (25.0)	6 (15.0)	0.3	10 (22.0)	7 (20.0)	0.8

Values are number (percentage). *One patient could have more than one lesion.

No association was found between HLA DRB1*1501 antigen status and the clinical features or EDSS score as well as between presence or absence of HLA DRB1*1501 and presence or absence of OCB in the present subset of patients with MS (OR, 1.58; 95% CI, 0.65 to 3.87; P=0.3). Progressive course of the disease tended to be more common than relapsing-remitting course in both OCB-positive and HLA DRB1*1501-positive patients with MS, although the difference was not significant (Table 2).

The presence of OCBs was associated with the presence of brainstem lesions and juxtacortical lesions on MRI (OR, 3.89; 95% CI, 1.45 to 10.37, and OR, 3.42; 95% CI, 1.33 to 8.77, respectively). The presence of HLA DRBI*1501 was associated only with brainstem lesions on MRI (OR, 2.60; 95% CI, 1.00 to 6.73). Table 3 shows the relationship of OCB and HLA DRBI*1501 with lesions on MRI.

Discussion

In the present study, 55% of all MS patients were positive for the OCBs and 56% for the HLA DRB1*1501. OCB-positive MS patients had higher IgG index, mean relapse rate, and EDSS scores than their OCB-negative counterparts. No relationship was found between HLA DRB1*1501 antigen status and the clinical features or EDSS score as well as between presence or absence of HLA DRB1*1501 and presence or absence of OCB in the present subset of MS patients.

The proportion of OCB-positive patients with MS in the present study was much smaller than that in Western European countries, where OCBs are found in 76%–90% of MS patients (6, 21, 22). It appeared to be much closer to those described in Oriental populations (55%–56%) (1, 12, 23, 24). These differences might be attributed to immunogenetic factors, which influence the intrathecal immune humoral functions and, at least in part, to different laboratory procedures and techniques (1, 12, 21–24). Although one of the most sensitive technique to test the presence of intrathecal specific OCB – isoelectric focusing and IgG specific immunofixation (19) – was applied in the present study, still such a finding in the Lithuanian population with MS is needed to be confirmed by other studies.

In the present study, the elevated IgG index was detected in nearly 53% of patients with MS, and it correlated well with positive OCBs. The IgG index is elevated (>0.6) in about 70%–90% of MS patients, and it is rarely abnormal in OCB-negative patients. The IgG index can be reduced to a reference value with steroid therapy, immunomodulation or immunosuppression, and decreased disease activity (14, 23, 25). Therefore, it has to be acknowledged that in some cases, CSF analysis was performed in the absence of disease activity.

The presence of OCBs was significantly associated with an increased number of exacerbations as well as with higher disability scores, while no associations between the presence of OCBs and the age at onset, gender, or course of the disease were found in the present study. These findings are consistent with the results presented by Siritho et al. and Koch et al., although in the last-mentioned study, a statement was made that positivity for OCBs indicated a more aggressive course of MS (14, 15). This was confirmed by later studies conducted in Italy and Portugal (26, 27). On the contrary, Idiman et al. showed that Turkish MS patients who were positive for OCBs had slower disease progression and better disease course with less disability (12).

The presence of OCBs was associated with more frequent lesions juxtacortically and in the brainstem on MRI scans. A study by Huttner et al. showed similar results as in the present study: OCB-positive patients had juxtacortical lesions more frequently (P=0.022), and OCB-negative patients showed a significantly lower prevalence of infratentorial lesions (P=0.005) (28).

In a Caucasian population, HLA DRB1*1501 allele is one of the most important genetic risk factors, associated with the development of MS (1, 11, 29). Only 56% of MS patients in the present study were found to have HLA DRB1*1501 allele. The frequency of HLA DRB1*1501 was higher in OCB-positive patients with MS than OCB-negative patients, but the difference was statistically insignificant (P=0.3). Nevertheless, this is in accord with the studies performed in Australia (1), Turkey (12), and Spain (22) where a higher frequency of HLA

DRB1*1501 allele was reported in OCB-positive patients than OCB-negative patients. No association was found between HLA DRB1*1501 and gender or age at onset. This is in conflict with several other studies reporting that the presence of DR15 was associated with younger age at diagnosis and female sex (9, 11, 30, 31). A relatively small sample of MS patients could be one of the reasons of such a situation. On the other hand, as in the present study, most surveys have found no association between HLA and disease outcome (11, 32, 33).

Our study has several limitations, which have to be mentioned. First, although it was a prospective study, some clinical data were gathered retrospectively from the medical records. Second, the data presented here were obtained from a relatively small group of MS patients, and this might have influenced partly inconclusive results. Therefore, this study should be judged as a pilot study, and the results have to be confirmed in the larger sample of Lithuanian MS patients.

Conclusions

The presence of oligoclonal bands in the cerebrospinal fluid of Lithuanian patients with multiple sclerosis was significantly associated with the greater number of exacerbations, higher degree of disability at onset and at the last visit, and higher IgG index. There were no significant associations between the presence of HLA DRB1*1501 allele and the clinical symptoms, course of disease, or disability score. An estimated tendency was observed for those who were positive for HLA DRB1*1501 and also positive for oligoclonal banding proving the hypothesis of the presence of isolated HLA DRB1*1501 haplotype to be insufficient and obligate for the disease development. Moreover, immunogenetic factors are very important for the clinical manifestations, natural course of the disease and, thus, gathering some information on the prognosis and future perspectives.

Statement of Conflict of Interest

The authors state no conflict of interest.

Žmogaus leukocitų antigeno DRB1*1501 ir oligokloninių juostų įtaka išsėtinės sklerozės klinikiniam pasireiškimui ir negaliai

Renata Balnytė[1], Daiva Rastenytė[1], Ingrida Ulozienė[2], Dalia Mickevičienė[1], Erika Skrodenienė[3], Astra Vitkauskienė[3]

[1]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Neurologijos klinika,
[2]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Ausų, nosies ir gerklės ligų klinika,
[3]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Laboratorinės medicinos klinika

Raktažodžiai: išsėtinė sklerozė, žmogaus leukocitų antigenas DRB1*1501, oligokloninės juostos, klinikiniai požymiai, negalia.

Santrauka. *Tyrimo tikslas.* Įvardyti imunogenetinių rizikos veiksnių reikšmę, jų galimą įtaką klinikiniam išsėtinės sklerozės pasireiškimui ir negalios atsiradimui sergantiesiems išsėtine skleroze Lietuvos populiacijoje.

Tyrimo medžiaga ir metodai. Atliktas perspektyvusis tyrimas su 80 sergančiųjų išsėtine skleroze. Diagnozė patvirtinta McDonaldo kriterijais. Oligokloninės juostos nustatytos naudojant izoelektrinio fokusavimo ir IgG imunofiksacijos metodą. HLA aleliai sergantiesiems išsėtine skleroze buvo nustatyti naudojant polimerazės grandininę reakciją.

Rezultatai. 55 proc. tiriamųjų rasta oligokloninių juostų, 56 proc. rastas HLA DRB1*1501 alelis. Sergantieji išsėtine skleroze, kuriems rasta oligokloninių juostų, turėjo didesnę negalią pagal EDSS ligos pradžioje, lyginant su tiriamaisiais, kuriems oligokloninių juostų nerasta (3,93±1,21 ir 3,36±0,96 balo, p=0,02) ir paskutinio vizito metu (4,31±2,06 ir 3,09±1,98 balo, p=0,009). Paūmėjimų dažnis buvo didesnis tiriamiesiems, kuriems rasta oligokloninių juostų, lyginant su grupe tiriamųjų, kuriems oligokloninių juostų nerasta (1,45±0,69 ir 0,58±0,64, p=0,001). Tiriamieji, kuriems rasta oligokloninių juostų, turėjo didesnį IgG indeksą lyginant su tiriamaisiais, kuriems oligokloninių juostų nerasta (p=0,0001). Nerasta ryšio tarp HLA DRB1*1501 ir klinikinių požymių, EDSS bei oligokloninių juostų turinčiais ir neturinčiais pacientais.

Išvados. Oligokloninės juostos, rastos sergančiųjų išsėtine skleroze smegenų skystyje, turėjo ryšį su didesniu paūmėjimų skaičiumi, didesne negalia ir didesniu IgG indeksu. HLA DRB1*1501 allelis nekoreliavo nei su klinikiniais simptomais, nei su ligos eiga ir negalia.

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