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Running head HLA and primary CNS lymphoma

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Abstract

Human leukocyte antigens (HLA) are involved in the regulation of immune response to infection and in malignant transformation. Several HLA alleles are associated with immunological or malignant diseases. The aim of the present study was to evaluate a potential association of HLA class I and II alleles with primary central nervous system lymphoma (PCNSL) in immunocompetent patients. We therefore analyzed particular HLA-A, HLA-B and HLA-DRB1 alleles in 82 PCNSL patients and compared the data to those in 327 population controls. No significant difference between these two groups was found using Pearson's chi^2 test. These data do not support the hypothesis that HLA alleles play a major role in the pathogenesis of PCNSL.

Keywords Alleles - HLA - Immunocompetent Patients - PCNSL

Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive subtype of non-Hodgkin's lymphoma (NHL) arising within the central nervous system (CNS) in the absence of systemic manifestations. The majority of these tumors are diffuse large B-cell lymphomas (DLBCL) derived from germinal center B cells [1]. PCNSL is known to be associated with immunodeficiency, for example, due to the acquired immunodeficiency syndrome (AIDS) or to long-term immunosuppressive therapy [2, 3]. In immunocompetent patients, an association of PCNSL with the germline genetic variant methyltetrahydrofolate homocysteine S-methyltransferase (MTR) c.2756A>G (p.D919G) has been reported [4].

Human leukocyte antigens (HLA) class I and II play an important role in regulating the immune response to infection and malignant transformation. Certain HLA alleles are associated with autoimmune diseases such as ankylosing spondylitis (B27) and multiple sclerosis (DR2, DQ3). Furthermore, HLA alleles have been reported to be associated with nasopharyngeal, colorectal and thyroid carcinoma [5, 6]. Findings are less clear for primary brain tumors such as glioma and meningioma [7, 8]. In malignant lymphoma, an association between HLA alleles and Hodgkin`s lymphoma, HTLV-1-associated T-cell-lymphoma and mycosis fungoides has been described [9-12]. However, the relevance of HLA alleles for the development of PCNSL has not been investigated yet.

Patients and methods

Between 08/2000 and 09/2002 a series of 82 consecutive immunocompetent PCNSL patients of Caucasian origin recruited for the ongoing German multicenter phase IV trial (G-PCNSL-SG-1) were evaluated. The aim of the G-PCNSL-SG-1 study was to analyze the value of whole brain radiotherapy in first-line therapy of patients with PCNSL. Inclusion criteria for the G-PCNSL-SG-1 study was a newly diagnosed and histologically or cytologically (in the cerebrospinal fluid) confirmed PCNSL in an immunocompetent patient with an adequate renal

and bone marrow function. Exclusion criteria were systemic manifestation of NHL and additional malignancies as well as immunodeficiency or concomitant immunosuppressive therapy. The median age of patients analysed for the present study was 59 years (range 18-76 years), 48% were female. Control blood samples were obtained from 327 healthy German Caucasian blood donors at the Department of Transfusion Medicine and at the Section of Transplantation-Immunology and Immunohematology, University of Tuebingen Medical Center. EDTA blood was drawn from all patients and controls after informed consent and stored at -20°C until analysis. The study was approved by the respective local ethics committees.

Genomic DNA was isolated from peripheral blood cells applying the QIAamp® Blood Kit (Qiagen, Chatsworth, CA, USA) [13]. The LiPA HLA-A/v1.5/010331, HLA-B/v1.5/010331 and HLA-DRB/v5.5/010331 sequence specific oligonucleotide (SSO) typing kits (Innogenetics, Brussels, Belgium) were applied for low/medium resolution HLA typing of the HLA-A, -B, -DRB1 alleles.

For statistical analysis HLA allele frequencies were determined in the patient group and compared to those of the local control sample. Comparisons between patients and control individuals were performed by Pearson's chi^2 test (degrees of freedom = 1) with Yates' correction for small sample sizes where applicable. Threshold was defined with two-sided $\alpha = 0.05$. All statistical calculations were performed using Statistical Analysis Software (SAS) Program for Windows, version 6.11.

Results and discussion

The status of particular HLA-A, -B and -DRB1 alleles was analyzed in 82 immunocompetent patients with PCNSL and 327 healthy control individuals in order to investigate whether there are associations between HLA alleles and PCNSL. The observed frequencies of the HLA alleles analyzed in the patient and the control sample are given in Table 1. Statistical analysis

did not reveal any significant differences in the frequencies of HLA-A, HLA-B and HLA-DRB1 alleles between these two groups.

Our results are limited by the sample size of PCNSL patients. However, a major effect of the analyzed HLA alleles on the development of PCNSL in this patient collective seems unlikely. The presented data therefore do not support the hypothesis of an involvement of HLA alleles in the pathogenesis of PCNSL in immunocompetent patients. Additional studies may be required to increase the power of this conclusion, and studies on immunocomprized and immunodeficient patients as well as the analysis of further HLA alleles may be added.

Acknowledgement

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Table 1 Human leukocyte antigen (HLA) allele frequencies in patients with primary central nervous system lymphoma (n = 82) and healthy control individuals (n = 327)

HLA-A				HLA-B				HLA-DRB1			
allele	**patients**	**controls**	**χ^2; *P***	**allele**	**patients**	**controls**	**χ^2; *P***	**allele**	**patients**	**controls**	**χ^2; *P***
01	0.30	0.29	0.165; 0.685[a]	07	0.27	0.24	0.414; 0.520[a]	01	0.17	0.24	0.377; 0.539[a]
02	0.48	0.48	0.184; 0.668[a]	08	0.24	0.20	0.390; 0.532[a]	03	0.21	0.22	0.091; 0.762[a]
03	0.18	0.30	2.344; 0.126[a]	13	0.02	0.04	0.187; 0.665[a]	04	0.15	0.27	1.849; 0.174[a]
11	0.12	0.13	0.003; 0.953	14	0.02	0.05	0.294; 0.588[a]	07	0.15	0.18	0.00; 0.995
23	0.06	0.03	0.902; 0.342[a]	15	0.18	0.14	0.745; 0.388[a]	08	0.08	0.08	0.112; 0.738[a]
24	0.11	0.16	0.405; 0.524[a]	18	0.07	0.09	0.040; 0.841[a]	09	0.0	0.02	0.222; 0.638[a]
25	0.02	0.04	0.051; 0.822[a]	27	0.12	0.09	0.393; 0.531[a]	10	0.01	0.02	0.008; 0.928
26	0.07	0.09	0.003; 0.957[a]	35	0.18	0.25	1.068; 0.301[a]	11	0.21	0.22	0.127; 0.722[a]
29	0.02	0.05	0.304; 0.581[a]	37	0.01	0.02	0.060; 0.807[a]	12	0.06	0.03	1.112; 0.292[a]
30	0.01	0.04	0.626; 0.429[a]	38	0.05	0.07	0.267; 0.606[a]	13	0.29	0.26	1.138; 0.286[a]
31	0.06	0.05	0.171; 0.679[a]	39	0.02	0.04	0.187; 0.665[a]	14	0.04	0.08	0.734; 0.392[a]
32	0.12	0.09	0.963; 0.326[a]	40	0.05	0.11	1.979; 0.159[a]	15	0.31	0.27	1.645; 0.200[a]
33	0.01	0.03	0.102; 0.750[a]	41	0.02	0.01	0.322; 0.570[a]	16	0.06	0.16	2.942; 0.086[a]
34	0.0	0.0		42	0.0	0.0		NA[b]	0.20	0.02	
66	0.02	0.01	0.905; 0.342[a]	44	0.26	0.20	1.147; 0.284[a]				
68	0.13	0.11	0.381; 0.537[a]	45	0.0	0.0					
69	0.0	0.01	0.010; 0.920[a]	46	0.0	0.0					
NA[b]	0.24	0.08		47	0.01	0.01	0.066; 0.798				
				48	0.0	0.0					
				49	0.02	0.02	0.132; 0.716				
				50	0.01	0.03	0.418; 0.518[a]				
				51	0.13	0.12	0.016; 0.898[a]				
				52	0.02	0.01	0.099; 0.753[a]				
				53	0.01	0.01	0.00; 0.995				
				54	0.0	0.0					
				55	0.0	0.03	1.411; 0.235[a]				
				56	0.01	0.01	0.00; 0.995				
				57	0.06	0.06	0.007; 0.931				
				58	0.01	0.01	0.066; 0.798				
				59	0.0	0.0					
				67	0.0	0.0					
				NA[b]	0.13	0.04					

[a] Yates correction for small sample size; [b] not assessable

Allele frequencies are given as relative amount.

P is the result of Pearson`s chi^2 test.