Meningioma: Is There an Association with Human Leukocyte Antigens?

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Abstract

The expression of human leukocyte antigen (HLA) alleles plays an important role in the development and recurrence of benign and malignant diseases. Association of single HLA alleles or haplotypes with neoplastic processes has been investigated previously, and correlation between HLA and solid tumors, such as head and neck cancers or uterine cervical squamous epithelial lesions, were reported. However, there is no published data on the influence of the HLA system on the development of symptomatic cerebral meningioma, a mostly benign intracranial tumor of mesenchymal origin in adults.

The present investigation is comparing the frequency of single HLA alleles and haplotypes in 81 adult Caucasian patients with symptomatic central nervous system meningiomas to that of 157 area- and race-matched healthy controls. Both standard serological and molecular genetic (PCR) techniques were used for HLA typing.

Our results suggest an association between single HLA alleles and occurrence of clinically symptomatic meningioma. Patients with *HLA-A*02* had a 2.5-fold increased risk of meningioma ($P = 0.02$), and those with *HLA-DQB1*05* had a 1.8-fold increased risk of meningioma ($P = 0.05$). Conversely, *HLA-A*01*, *-B*08*, and *-DRB1*03* were associated with a 0.4-, 0.5-, and 0.5-fold, respectively, decreased risk of meningioma ($P = 0.008$, $P = 0.05$, and $P = 0.04$). Moreover, the occurrence rate of combinations and estimated haplotypes containing these HLA alleles was strikingly different in meningioma patients compared with controls: significantly increased for the haplotypes *HLA-A*02:DRB1*04* ($P = 0.02$, relative risk = 2.5) and *HLA-A*02:DRB1*04:DQB1*0302,DQB1*05* ($P = 0.03$, RR = 7.5), and significantly decreased for the haplotype *HLA-A*01:B*08:DRB1*03* ($P = 0.01$, relative risk = 0.2).

In conclusion, these data suggest that some single HLA alleles and haplotypes may protect from or predispose to developing symptomatic central nervous system meningioma during adult life. These associations may be indicative of the involvement of the immune system in the host antitumor surveillance, recognition, and destruction of *de novo* arising human tumor cells.

Introduction

Meningiomas are mostly benign and relatively slow growing neoplasms descending from the arachnoideal membrane and rarely displaying biologically aggressive behavior such as invasion of surrounding nonmeningial tissue. They represent 13–18% of all primary intracranial tumors, and have an incidence of ~6 cases/100,000 of the population per year and a female: male ratio of 2:1 (1, 2). The precise etiology of meningiomas remains unknown, but some factors thought to predispose to their development are trauma, ionizing radiation, neurofibromatosis type II, chromosome 22 aberrations, and female hormones. The need for reliable risk calculation factors and prognostic criteria for these tumors has been widely recognized, and many authors have attempted to define parameters that may discriminate persons more susceptible to meningioma, and more prone to the molecular and immune phenomena that drive meningioma progression (3–7).

Human leukocyte antigens (HLA) are widely expressed cell surface molecules that present antigenic peptides to T lymphocytes, and modulate the immune response against inflammatory and malignant diseases. HLA polymorphism is known to alter disease susceptibility and progression in a range of inflammatory and malignant conditions (8). The HLA phenotype is assumed to modulate cytokine levels that play a role in T-cell activation (9, 10), and was shown to be associated with tumor response to cytokines as well as represent a background for oncogenic recognition (11–15). Since the first demonstration of correlation between human HLA and disease (reviewed in Refs. 16, 17), investigations of the influence of single HLA alleles or HLA haplotypes on the risk of disease steadily increased (18–20). Some strong correlations between HLA and benign chronic diseases have been reported, such as *HLA-B27* in ankylosing spondylitis, *HLA-DRB1*03* and *HLA-DRB1*04* in diabetes mellitus, as well as *HLA-DRB1*04* and *HLA-DRB1*01* in rheumatoid arthritis (reviewed in Refs. 8, 16). In the case of ankylosing spondylitis, an association between the occurrence of *HLA-B27* and disease has been detected in >90% of all patients (21). Positive and negative associations between single *HLA-DR* and *-DQ* alleles or haplotypes and other diseases, such as intermediate uveitis, cervical intraepithelial neoplasia, or multiple sclerosis, have been reported (22–24). A strong association was found between *HLA-DR2* (now known as the splits *HLA-DRB1*15* and *HLA-DRB1*16*) and narcolepsy (25).

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Table 1 Age, gender, and tumor grade of patients

WHO grading of tumor	Number of patients	Female	Male	Mean age
G I	56	40	16	62.5 ± 3.0
G II	21	6	15	56.9 ± 4.0
G III	4	2	2	47.0 ± 20.0
Total	81	48	33	60.4 ± 3.0

To our knowledge, there are no studies published previously exploring the association of central nervous system (CNS) meningioma with the HLA system. Primary brain tumors (gliomas), on the other hand, have been investigated previously in Japanese patients (26, 27) and in Caucasian patients from Switzerland (28), Germany (29), and Italy (30). Anecdotal studies in patients with other types of brain tumors (*e.g.*, primary CNS lymphomas) have been also carried out (31).

The present prospective study was aimed at investigating a group of adult Caucasian patients from Germany with symptomatic intracranial meningiomas, and at comparing the findings to area- and race-matched asymptomatic controls.

Materials and Methods

Study Population. Eighty-one genetically unrelated consecutive patients with clinically and radiologically diagnosed intracranial meningiomas (WHO grades I-III) were enrolled in the study after signing an informed consent. All of the patients subsequently underwent surgery for tumor removal. Age, gender, and tumor grading data of the patient group are summarized in Table 1. All of the patients were German Caucasians from the German federal states of Saxony-Anhalt and Thuringia. For HLA typing, peripheral blood was drawn from each patient before tumor surgery. Histopathologic diagnosis and grading of the tumor was done on paraffin-embedded surgical specimens according to the WHO criteria (3). The patients group was compared with a control group consisting of 157 randomly selected healthy Caucasian German blood donors from the same area. Both groups were screened for chronic diseases such as diabetes mellitus, polyarthritis, ankylosing spondylitis, and multiple sclerosis. Except for a diabetic type of metabolism caused by high doses of steroids in meningioma patients, none of the above diseases was present in either group. Also control individuals were asymptomatic for any type of brain tumor at the time of screening and up to 3 years afterwards.

Serological HLA Typing. After separating peripheral blood leukocytes by density gradient centrifugation, serological typing by standard NIH microlymphocytotoxicity test (32) was performed for *HLA-A*, *-B*, and *-Cw* antigens in accordance with the manufacturer's instructions (Lymphotype 144; Biotest AG, Dreieich, Germany, and Histotype 144; BAG, Lich, Germany).

Genomic HLA Typing. Genomic DNA was extracted from peripheral blood leukocytes of each individual and amplified by PCR using a thermocycler PE 9600 (Perkin-Elmer, Weiterstadt, Germany; Ref. 33). All of the patients and controls were typed by standard PCR- sequence-specific primer low resolution technique using primer kits for *HLA-A*, *-B*, and *-Cw* typing (Deutsche Dynal AG, Hamburg, Germany), and for *HLA-DRB1*, *-DRB3/4/5*, and *-DQB1* typing (BAG and Deutsche Dynal AG).

Using combined serological and genomic HLA typing, we were able to determine all of the known low-resolution HLA alleles, *i.e.*, 24 *HLA-A*, 48 *HLA-B*, 17 *HLA-Cw*, 24 *HLA-DRB1*, 3 *HLA-DRB3/4/5*, and 7 *HLA-DQB1* alleles. The results of the serological and genomic *HLA-A*, *-B*, and *-Cw* typing were fully concordant.

Quality Control. HLA typing quality was proved by the typing of control samples from INSTAND (Institut für Standardisierung und Dokumentation in medizinischen Laboratorien e.V., Duesseldorf, Germany), German DNA Exchange (Prof. Ekkehard Albert, University of Munich, Munich, Germany), and International DNA Exchange (University of California Los Angeles Tissue Typing Laboratory, Los Angeles, CA).

Statistical Analysis. Statistical analysis of HLA types was based on contingency tables and performed by χ^2 test (p) with Yates continuity correction (p_c) to more closely approximate the data to the χ^2 distribution, or by Fisher's exact test (p_f) for frequencies ≤ 5 (when a χ^2 test is not appropriate, *i.e.*, $n \leq 5$; Refs. 34–36). Because of the lack of previous studies allowing for a specific hypothesis to be tested, *P*s were corrected according to the multiple comparison Bonferroni test (p_b), *i.e.*, by multiplication with the number of tested alleles of the respective HLA locus (34). A $P < 0.05$ was considered statistically significant. In the present study, only *P*s were cited that remained significant after applying the most conservative statistical correction method. Because haplotypes were not identified by family HLA typing, phenotypic combinations of antigens coded by different loci were used as estimated haplotypes. Two- and three-locus combinations were evaluated, which is a legitimate and often used way for analysis (37, 38). Statistical analysis of the estimated haplotypes was performed as described above. Furthermore, to assess the strength of an association, the relative risk (RR = ad/bc) of an observed phenotypic association was calculated. For frequencies <5, the Haldane modified formula was used: $RR_h = (2a+1)(2d+1)/(2b+1)(2c+1$; Ref. 39).

Results

Frequency of Single HLA Alleles. The frequency of the HLA alleles *HLA-A*02* ($p_b = 0.02$) and *HLA-DQB1*05* ($P = 0.05$) was significantly increased in the patient population compared with control individuals. On the other hand, the frequencies of *HLA-A*01* ($p_c = 0.008$), *HLA-B*08* ($P = 0.05$), and *HLA-DRB1*03* ($P = 0.04$) were decreased significantly in meningioma patients compared with controls. (Table 2) The *HLA-A*02* allele, in particular, retained its statistical significance even after the rigid Bonferroni correction with correction factor considering the *HLA-A* locus alleles themselves rather than the number of tests performed on the numerous estimated haplotypes (Table 3).

Table 2 Single human leukocyte antigen (HLA) alleles with statistically different frequency of occurrence in meningioma patients compared to control individuals

HLA	Controls (%) ($n = 157$)	Patients (%) ($n = 81$)	*P*	Relative risk
*A*01*	31.8	14.8	0.008[a]	0.4
*A*02*	48.4	70.4	0.02[b]	2.5
*B*08*	21.7	11.1	0.05	0.5
*DRB1*03*	24.8	13.6	0.04	0.5
*DQB1*05*	28.0	40.7	0.05	1.8

[a] Yates correction.
[b] Bonferroni correction.

Table 3 Frequency of selected human leukocyte antigen (HLA) combinations and estimated haplotypes in meningioma patients compared with control individuals

HLA	Controls (%) (n = 157)	Patients (%) (n = 81)	P	Relative risk
*DQB1*05,DQB1*0302*	1.3	6.2	0.03	4.5[b]
*A*02:DRB1*04*	10.2	22.2	0.02[a]	2.5
*A*02:DQB1*05*	13.4	29.6	0.004[a]	2.7
*A*02:DQB1*0302*	7.6	18.5	0.02[a]	2.7
*A*02:DRB1*04,DQB1*05*	1.3	8.6	0.01[a]	6.3[b]
*A*02:DRB1*04:DQB1*0302*	7.6	17.3	0.04[a]	2.5
*A*02:DRB1*04:DQB1*0302,DQB1*05*	0.6	6.2	0.03[a]	7.5[b]
*A*01:B*08*	17.8	3.7	0.004[a]	0.2[b]
*A*01:DQB1*02*	18.5	3.7	0.003[a]	0.2[b]
*A*01:B*08:DRB1*03*	14.0	2.5	0.01[a]	0.2[b]
*A*01:DRB1*03:DQB1*02*	15.3	2.5	0.005[a]	0.2[b]

[a] Yates correction.
[b] Haldane method.

Frequency of Combinations of HLA Locus Alleles and Estimated Haplotypes. Analyzing the combinations and estimated haplotypes, the above-discussed single HLA alleles were reconfirmed in their statistical significance. In some estimated HLA haplotypes *HLA-A*02* was expressed in higher frequency in the patient group. Such were *A*02:DRB1*04* (p_c = 0.02), *A*02:DQB1*05* (p_c = 0.004), *A*02:DQB1*0302* (p_c = 0.02), the extended estimated haplotype *A*02:DRB1*04:DQB1*0302* (p_c = 0.04), and the combination *A*02:DRB1*04,DQB1*05* (p_c = 0.01; Table 3). A significantly increased frequency of the combination *HLA-DQB1*05,DQB1*0302* (P = 0.03) was also demonstrated in the patients group (Table 3).

Conversely, compared with the control group, *HLA-A*01* was significantly less frequent in patients with the estimated haplotypes *HLA-A*01:B*08* (p_c = 0.004) and *HLA-A*01:B*08:DRB1*03* (p_c = 0.01), as well as *HLA-A*01:DQB1*02* (p_c = 0.003) and *HLA-A*01:DRB1*03:DQB1*02* (p_c = 0.005).

Whereas *HLA-DRB1*03* was significantly decreased (P = 0.04) and *HLA-DQB1*05* was significantly increased (P = 0.05), in none of the patients could both of the above be found simultaneously. Among the controls, on the other hand, in 7.6% of cases both alleles were expressed at the same time (p_c = 0.03).

No statistically significant HLA differences were found if patients were stratified according to gender and compared with gender-matched control individuals (data not shown).

Discussion

This study demonstrated significant correlations of single HLA alleles with the occurrence of symptomatic CNS meningioma in adult German patients of the Caucasian white race. Due to possible geographical differences in racial and genetic background, only locally resident and therefore supposedly genetically homogeneous groups of patients and controls were investigated.

Our study showed that individuals expressing the alleles *HLA-A*02* and *-DQB1*05* may be at higher risk for developing disease (RR, 2.5 and 1.8, respectively), whereas the RR of individuals expressing *HLA-A*01*, *HLA-B*08*, or *HLA-DRB1*03* seems to be decreased (RR, 0.4, 0.5, and 0.5, respectively).

Some HLA combinations and estimated haplotypes may be prevalent in persons developing symptomatic intracranial meningioma during their adult life. The data presented here suggest that there are single HLA alleles that stand for a disease-prone phenotype, and that the RR for the occurrence of disease increases if these single HLA alleles are associated with defined haplotypes. Thus, individuals with *HLA-A*02* in combination with *HLA-DRB1*04*, *HLA-DQB1*05*, or *HLA-DQB1*0302* seem to develop meningiomas significantly more often (RR_h, 2.7). In addition, the simultaneous occurrence of *HLA-DQB1*05* and *HLA-DQB1*0302* in a combination increases the risk (RR_h) of meningioma to a value of 7.5.

It should be emphasized that, considering the above-mentioned extended haplotypes, findings should be interpreted with great caution due to the relatively small sample sizes. Nevertheless, the available data were analyzed with utmost statistical stringency, and the results suggest that susceptibility for meningioma may be associated with certain HLA combinations and haplotypes, as well as with some single HLA alleles.

The association of HLA alleles with solid tumors, such as nasopharyngeal, colorectal, or thyroid carcinoma have been described previously (18, 40–42). *HLA-B*18* was increased significantly in Malay patients with nasopharyngeal carcinoma (40) and in patients diagnosed with colorectal cancer in a Greek study (41). Similar to the meningioma patients in the present study, the frequency of *HLA-A*02* was increased among Chinese patients with nasopharyngeal carcinoma (43). Romano *et al.* (44) reported a significant association between *HLA-DR7* (now designated as *HLA-DRB1*07*) and resistance to lung cancer, which is in accordance with findings in glioma patients (29), whereas Sridama *et al.* (42) showed a significant increase of *HLA-DR7* in thyroid cancer patients. On the other hand, Hildesheim *et al.* (19) described a negative association of *HLA-DRB1*1501:DQB1*0602* with cervical neoplasia. Other studies (23, 45) suggested that *HLA-DRB1*1501* and *HLA-DQB1*0602* may rather increase the risk of uterine cervix neoplasia. A recent study in the same disease found a reduced risk of progression associated with the single allele *HLA-Cw*0202* (46).

Concerning CNS tumors, there have been investigations on gliomas in groups of Japanese, German, and Swiss patients which, however, yielded some inconsistent findings (26–31). Whereas Takai *et al.* (26) and De Moerloose *et al.* (28) found increased *HLA-B61/62* and *-B35*, respectively, Nitta *et al.* (27) and Machulla *et al.* (29) reported a higher frequency *of HLA-A24* and *-A25*. Ferrante *et al.* (30) found *HLA-A03* increased in patients with neuroepithelial brain tumors. Despite the above differences, alleles such as *HLA-A*03* and *HLA-DRB1*15* are frequently represented in a haplotype (*A*03:B*07:DRB1*15*). *HLA-A*03* and *HLA-B*35* are also included in another fre-

quently found haplotype (*A*03:B*35:DRB1*01*). Finally, similarly to our study, Herrlinger *et al.* (31) suggested a protective influence of the haplotype *HLA-A*01:B*08:DRB1*03* in primary CNS lymphoma.

Despite the actual amount of published data, there is no real consent yet on the existence of an established correlation of specific HLA alleles with the increased or decreased RR of solid tumors. The interpretation and comparison of the published findings is difficult, at least in part because the association studies are based on different types of tumors. Also, at least in theory, asymptomatic controls may develop a clinically symptomatic meningioma in later life. Given the known incidence of 6 new cases per 100,000 of the population per year, however, the above possibility would still result in a negligible tumor incidence in the control group.

In conclusion, this study demonstrates the possibility of association between the expression of some HLA alleles and the occurrence of clinically symptomatic meningioma in a nonselected group of adult patients. The statistically significant differences in the frequency of HLA alleles in meningioma patients and healthy control individuals may suggest an involvement of HLA in the development and progression of intracranial meningioma. Given the relationship between HLA antigens and their appropriate receptors on T lymphocytes and natural killer cells, the association observed in meningioma cases may indicate the role of the host cellular immune response in recognizing and destroying meningioma cells.

The predictive value of single HLA alleles or HLA haplotypes and combinations should be studied further in a much larger population of patients. To exclude possible bias due to clinically silent and undetected but nevertheless intrinsically developing meningiomas, control individuals need to be followed for at least 10 years for tumor occurrence.

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