Original Article

Meningioma and Expression of Human Leukocyte Antigen-B5, 7, 8, 27, and 51: Is there any Relevance?

Abstract

Background: Cerebral meningiomas are among the most prevalent brain tumors. Most cases of cerebral meningioma are benign and respond well to the treatment. However, there is no conclusive laboratory method for screening of such tumors. Given the lack of a screening approach for meningiomas, we examined the expressions of human leukocyte antigen (HLA)-B5, 7, 8, 27, and 51 in patients with cerebral meningioma in this research in order to achieve a reliable laboratory parameter in this regard. **Materials and Methods:** Patients with cerebral meningioma who referred to Golestan Hospital, namely one of the largest neurosurgery centers in the southwest of Iran, were identified and examined over a 2-year period. After confirmation of cerebral meningioma diagnosis, the patients were enrolled in the study. **Results:** There was no significant relationship between the expressions of the abovementioned HLAs with platelet parameters, lymphocyte, monocyte, and neutrophil counts, clinical manifestations, family history, drug consumption, and alcohol abuse. A higher expression level of HLA-B5 was observed in the patients. **Conclusion:** With regard to the expression of HLA-B5 in nearly one-third of patients, it is likely to use this antigen or its serotype, namely HLA-B51, as a laboratory marker for screening of disease in the future through the study of larger populations.

Keywords: *Brain tumor, human leukocyte antigen, meningioma*

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Introduction

Meningioma is the most frequent primary brain tumor, which is currently treated by surgery resection,[1] although systemic therapy (such as chemotherapy) or radiotherapy can also be used depending on the site of tumor and the extent of resection. Meningiomas account for approximately 30% of central nervous system (CNS) tumors and 5% of tumors in children and adolescents, the prevalence of which increases with the increase in age. The disease is accidentally diagnosed in the third and sixth decades of life and is more common in women than in men.[1,2] Unfortunately, there is limited epidemiological information about this disease in Iran. However, a number of neurosurgical centers have published significant statistics in recent years and cited their epidemiological data. For instance, Mehrazin *et al*. retrospectively studied 3437 patients with brain tumor who were admitted to neurosurgical center of Shariati Hospital between 1978 and 2003. Their study showed that meningioma was the most frequent type of brain tumor that was diagnosed in 26% of patients. Most patients (86%) were in the age range of 21–65 years, and the prevalence was higher in women compared with men (32.7 vs. 19.7%).[3] Jazayeri *et al*. conducted a systemic review in 2014 and examined nine articles along with the Iranian National Cancer Registry data. The data covered a period of 10 years (2000–2010), and a review of over 9000 patients revealed that meningioma was the most common type of brain tumor in patients with an annual incidence rate of 1.58 cases per 100,000 population.[4] Taken together, these data suggest that the prevalence of meningioma in Iran is in agreement with world records; however, the need for new data for epidemiologic studies is strongly felt. Although meningioma is a common neoplasm, metastasis is a rare phenomenon in this tumor that is often benign; nevertheless, nearly 20% of cases show invasive clinical features leading to the death of patients.[5] Meningiomas often stem

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from arachnoid layer cells with high metabolic activity that are involved in cerebrospinal fluid reabsorption.[2] According to a histopathologic classification presented by the World Health Organization (WHO), meningioma has three grades: Grade I (benign), Grade II (atypical), and Grade III (anaplastic); Grade I is more common, but Grades II and III are mostly observed in men. Despite the rarity of the disease among children and adolescents, meningioma tends to be more invasive in them and presents in association with hereditary syndromes such as type 2 neurofibromatosis.[6,7] Cerebral meningioma was among the first solid neoplasms subjected to cytogenetic study, so that the role of chromosome 22 monosomy syndrome, hormone receptors, and edema due to growth factors has been considered in this disease. In 2000, the WHO for the first time presented genetic results along with histopathologic and immunohistochemistry findings to classify cerebral meningioma.[8] The diagnosis of meningioma was previously reliant on clinical symptoms, but it is now easily diagnosed with the advent and spread of new imaging technologies. However, attention to clinical symptoms can be helpful given their association with the site of cranial involvement. For example, patients with parasagittal meningioma, which mainly occurs in the frontal lobe, show Jacksonian seizure in lower extremities as well as headache, whereas those with meningioma in the anterior base of the cranium are affected with visual impairment in over 50% of cases.[9,10] In computed tomography (CT) and magnetic resonance imaging (MRI) images of cerebral meningioma patients, the isodense masses associated with dural surfaces (called dural tail signs) exhibit a mottling structure, which is caused by high vascularization and is a characteristic finding in these images.[2] Previous studies have indicated 50 and 90% sensitivity and specificity of dural tail sign structures, respectively.[11] As mentioned, patients often have benign tumors and their main treatment is surgery, which shows satisfactory results due to extensive advancement of neurosurgical techniques. Nevertheless, no specific screening for meningioma has been introduced so far.[2] Human leukocyte antigen (HLA) is widely expressed on different molecules and presents antigenic peptides to T-lymphocytes, thereby regulating the immune response in inflammatory and malignant diseases; therefore, HLA is capable of changing disease susceptibility and progression in a range of inflammatory and malignant conditions.[12,13] HLA appears to play an essential role in the activation of T-cells by regulating cytokine levels,[14,15] and it is also associated with tumor response to cytokines.[16-20] The research concerning the effect of HLA on risk of developing various diseases is steadily increasing.[21] In addition to the essential role of these antigens in the immune response process, their prognostic role in autoimmune diseases and cancer has been emphasized.[22,23] Tissue transplantation in CNS is not normally affected by the immune system, so the brain can be considered as an immunologically privileged site.[24] On the other hand, several studies have examined the role of HLA in patients with glioma.[25-29] In this research, we aimed to investigate patients with meningioma, their complete blood count (CBC) indices, as well as the expression of a number of HLAs including HLA-B5, 7, 8, 27, and 51 to evaluate the likelihood of using these antigens as prognostic/screening factors.

Materials and Methods

Ethics

All the procedures performed in the studies involving human participants were in agreement with ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR. AJUMS. REC.1397.220) as well as 1964 Helsinki Declaration.

Selection of participants

In this study, patients referring to Ahvaz Golestan Hospital (neurological center in the southwest of Iran) from April 2017 to April 2019 showing symptoms associated with brain tumor were subject to clinical and laboratory examination, CT scan, MRI, and surgery to provide samples for pathological examination. Following operation and preparation of sample, laboratory analysis was performed and 27 patients with definite diagnosis of meningioma were enrolled after written informed consent, confirmation of meningioma by a pathologist, and rejection of other possible factors [Table 1]. The following data were obtained along with a blood sample from patients to assess CBC for epidemiological study: age, sex, presence or absence of clinical symptoms at the time of diagnosis, CBC data after confirmation of meningioma, and family history.

Statistical analysis

In this study, data were expressed as mean ± SD. Analysis of data was performed using the *t*-test or its nonparametric equivalent (Mann–Whitney), Chi-square test and (if necessary) Fisher's exact.

The software used in this research was IBM SPSS Edition 22 (IBM Corporation, Armonk, NY, USA). To examine the initial assumptions, Kolmogorov–Smirnov test was performed in order to verify the normal distribution of data at a significance level of 0.05 where $P < 0.05$ indicated that the data had not normal distribution. In all tests, a significance level of $P < 0.05$ was considered.

Sampling and human leukocyte antigen typing

To examine the expressions of HLAs in patients, 7 ml of venous blood was drawn in tubes containing heparin anticoagulant to prevent membrane degradation that leads to false-positive results. We used standard lymphocytotoxicity HLA typing and HISTO TRAY Disease HLA I Class Kit (BAG HEALTHCARE, Lich, Germany) to evaluate the expressions of HLAs. To assess CBC parameters and their

Table 1: Patients' human leukocyte antigen expression and laboratory data

Characteristics	Patients (*n*=27)
Sex, *n* (%)	
Male	6 (22)
Female	21 (78)
Age (mean±SD) (range)	54
PLT (×10^3/uL) (mean±SD)	227.66±64.7
RBC (×10^6/uL) (mean±SD)	4.78±0.47
WBC (×10^3/uL) (mean±SD)	7.37±1.46
PDW (%) (mean±SD)	16.07±0.47
MPV (fl) (mean±SD)	8.92±1.11
Hb (g/dL) (mean±SD)	12.89±1.30
HCT (%) (mean±SD)	39.72±3.50
Lymphocyte (×10^3/uL) (mean±SD) (%)	2.59±0.70
Neutrophil (×10^3/uL) (mean±SD) (%)	4.04±0.87
Monocyte (×10^3/uL) (mean±SD) (%)	0.50±0.12
HLA-B7, *n* (%)	
Positive	2 (7.4)
Negative	25 (92.6)
HLA-B8, *n* (%)	
Positive	2 (7.4)
Negative	25 (92.6)
HLA-B27, *n* (%)	
Positive	3 (11.1)
Negative	24 (88.9)
HLA-B5, *n* (%)	
Positive	9 (33.3)
Negative	18 (66.7)
HLA-B51, *n* (%)	
Positive	5 (18.5)
Negative	22 (81.5)

RBC: Red blood cell, WBC: White blood cell, PLT: Platelet, PDW: PLT distribution width, MPV: Mean PLT volume, Hb: Hemoglobin, HCT: Hematocrit, HLA: Human leukocyte antigen, SD: Standard deviation

relationship with antigen expression, 2 ml of venous sample was taken in ethylenediaminetetraacetic acid-anticoagulated tubes to maintain cell morphology.

Isolation of lymphocytes

Before evaluation of HLA expression, it is necessary to isolate lymphocytes from other cells in samples, especially platelets. In order to isolate lymphocytes, 10 mL venous blood sample was collected in heparin-anticoagulated tubes. 4 mL Ficoll was added to 6 mL of defibrinated blood sample. The sample was centrifuged at 1500 rpm for 20 min and then washed with Hanks' solution three times. After the washing step, 1 µL suspension and 1 µL HLA antiserum were added to each well of plate using Hamilton syringes, and the plates were incubated in room temperature (RT) for 30 min. After incubation, 5 µL complement was added to each well, and once more, the plates were incubated in RT for 60 min. After the last incubation step, eosin dye and formalin were added to plates. Finally, the expression of HLAs was evaluated using inverted microscope [Figure 1].

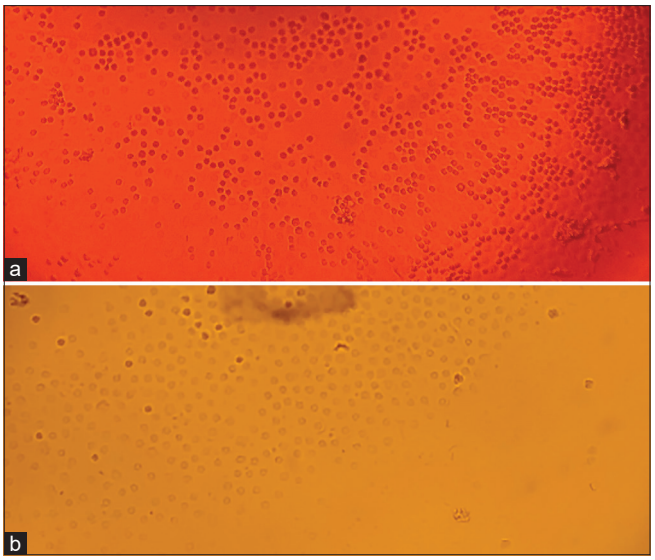

Figure 1: Human leukocyte antigen expression evaluation with inverted microscope. (a) Positive expression (dark spheres are dead lymphocytes); (b) Negative expression (colorless spheres are live lymphocytes)

Results

Expression of human leukocyte antigens

Considering the antigens under study, most of our patients were positive for HLA-B5 (33.3%) and HLA-B51 (18.5%), and only 11.1% of them had HLA-B27. A few patients were positive for other antigens as follows: HLA-B7 (7.4%) and HLA-B8 (7.4%). Mann–Whitney test revealed no significant correlation between the expressions of the more common HLA-B5 with mean platelet count (PLT) (P = 0.918), mean platelet volume (MPV) (P = 0.662), and platelet distribution width (PDW) (P = 0.938) in positive and negative patients [Table 2].

The evaluation of HLA-B5, which had a higher expression level, showed no correlation with mean monocyte (P = 1), lymphocyte (P = 0.258), and neutrophil (P = 0.269) counts neither in positive nor in negative groups. Other antigens did not show a significant relationship either [Table 3].

Comparison of different human leukocyte antigen expressions with clinical and laboratory data

There was no significant correlation between the expressions of HLAs with the presence or absence of clinical manifestations, family history, tumor relapse, and history of drug consumption by patients [Tables 4-6]. Twenty-seven patients were recruited in this study. Among the five tested antigens, HLA-B5 had the highest expression level among patients (33.3%). However, no significant association was found between the expressions of any of the antigens with different CBC parameters. There was no correlation between the

Table 2: Human leukocyte antigens' association with platelet counts and parameters

Antigens	Patients	MPV		PLT		PDW		Test
		Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*	
HLA-B7	Positive	8.35±0.78	0.478	288.00±15.55	0.127	15.70±0.00	0.226	Mann-Whitney
	Negative	8.97±1.14		222.84±64.86		17.20±0.48		
HLA-B8	Positive	8.20±0.99	0.321	271.00±29.70	0.405	15.70±0.35	0.328	
	Negative	8.98±1.13		224.00±65.87		16.08±0.48		
HLA-B27	Positive	8.37±0.99	0.334	212.00±81.83	0.817	15.93±0.49	0.461	
	Negative	8.99±1.13		229.62±64.22		16.07±0.48		
HLA-B5	Positive	8.86±1.36	0.662	229.44±63.18	0.918	16.10±0.56	0.938	
	Negative	8.95±1.02		226.77±67.34		16.03±0.45		
HLA-B51	Positive	9.64±1.35	0.134	218.80±79.49	0.950	16.40±0.53	0.102	
	Negative	8.76±1.03		229.68±62.99		15.98±0.44		

PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, SD: Standard deviation, HLA: Human leukocyte antigen

Table 3: Human leukocyte antigens' association with white blood cell counts

Antigens	Patients	Monocyte		Lymphocyte		Neutrophil		Test
		Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*	
HLA-B7	Positive	0.63±0.085	0.164	3.38±0.87	0.138	3.63±1.36	0.643	Mann-Whitney
	Negative	0.49±0.124		2.53±0.67		4.07±0.86		
HLA-B8	Positive	0.44±0.07	0.516	1.98±0.17	0.195	3.48±0.24	0.211	
	Negative	0.50±0.13		2.64±0.71		4.09±0.90		
HLA-B27	Positive	0.51±0.15	1.000	2.76±0.61	0.799	4.40±0.65	0.437	
	Negative	0.50±0.13		2.58±0.72		4.00±0.88		
HLA-B5	Positive	0.50±0.13	1.000	2.80±0.60	0.258	4.26±0.69	0.269	
	Negative	0.50±0.13		2.50±0.74		3.93±0.95		
HLA-B51	Positive	0.55±0.14	0.411	2.91±0.79	0.314	4.50±0.69	0.146	
	Negative	0.49±0.12		2.52±0.68		3.94±0.89		

HLA: Human leukocyte antigen, SD: Standard deviation

Table 4: Human leukocyte antigens' associations with clinical presentations

Antigens	Patients	Clinical presentation			Test
		Negative, *n* (%)	Positive, *n* (%)	*P*	
HLA-B7	Positive	0 (0)	2 (8)	1.000	Fisher's exact
	Negative	2 (100)	23 (92)		
HLA-B8	Positive	1 (50)	1 (4)	0.145	
	Negative	1 (50)	24 (96)		
HLA-B27	Positive	0 (0)	3 (12)	1.000	
	Negative	2 (100)	22 (88)		
HLA-B5	Positive	1 (50)	8 (32)	0.411	
	Negative	1 (50)	17 (68)		
HLA-B51	Positive	0 (0)	5 (20)	1.000	
	Negative	2 (100)	20 (80)		

HLA: Human leukocyte antigen

expressions of HLA-B5 with platelet parameters, including PLT ($P = 0.918$), MPV ($P = 0.334$), and PDW ($P = 0.938$). No relationship was found between the expressions of HLA-B5 (which showed a higher incidence in our patients) with monocyte ($P = 1$), lymphocyte ($P = 0.258$), and neutrophil counts ($P = 0.269$). There was no significant correlation between clinical manifestations ($P = 0.411$), family history ($P = 1$), tumor relapse ($P = 0.333$), and consumption of drug ($P = 0.411$). Our patients were in the age range of 31–77 (mean, 54 years), and the number of women was approximately four times that of men (21 women and 6 men).

Discussion

Cerebral meningiomas, which were first described by Swiss physician Felix Plater in 1614, generally originate from cells in the arachnoid mater (meningothelial cells), which surround the dura mater and account for nearly one-third of primary intracranial tumors.[30] The prevalence of these tumors increases with age, but they can occur at any age and are the most common primary cranial tumors with a higher frequency in women than relative to men.[31,32] The annual incidence of cerebral meningioma is estimated to be equivalent to 6 per 100,000 population.[33] Fortunately, these tumors are benign in 90% of cases and have a good prognosis after treatment.[34] Meanwhile, 10% of cases are malignant and show invasive manifestations, among which atypical meningioma is more prevalent and responsible for 4.7%–7.2% of total meningioma cases.[35] Subtypes of meningioma appear to be more common in men.[36] Before 2000 and initial presentation of meningioma classification guidelines by the WHO, the pathologic categorization of these types of brain tumors was highly assorted, which

Table 5: Human leukocyte antigens' associations with familial history and tumor relapse

Antigens	Patients	Tumor relapse			Familial history			Test
		Negative, *n* (%)	Positive, *n* (%)	*P*	Negative, *n* (%)	Positive, *n* (%)	*P*	
HLA-B7	Positive	2 (7.7)	0 (0)	1.000	2 (9.1)	0 (0)	1.000	Fisher's exact
	Negative	24 (92.3)	1 (100)		20 (90.9)	5 (100)		
HLA-B8	Positive	2 (7.7)	0 (0)	1.000	2 (9.1)	0 (0)	1.000	
	Negative	24 (92.3)	1 (100)		20 (90.9)	5 (100)		
HLA-B27	Positive	3 (11.5)	0 (0)	1.000	1 (4.5)	2 (40)	0.079	
	Negative	23 (88.5)	1 (100)		21 (95.5)	3 (60)		
HLA-B5	Positive	8 (30.8)	1 (100)	0.333	7 (31.8)	2 (40)	1.000	
	Negative	18 (69.2)	0 (0)		15 (68.2)	3 (60)		
HLA-B51	Positive	4 (15.4)	1 (100)	0.185	4 (18.2)	1 (20)	1.000	
	Negative	22 (84.6)	0 (0)		18 (81.8)	4 (80)		

HLA: Human leukocyte antigen

Table 6: Human leukocyte antigens' associations with drug use history of patients

Antigens	Patients	Drug consumption use		
		Negative, *n* (%)	Positive, *n* (%)	*P*
HLA-B7	Positive	2 (12.5)	0 (0)	0.499
	Negative	14 (87.5)	11 (100)	
HLA-B8	Positive	2 (7.4)	2 (7.4)	0.157
	Negative	25 (92.6)	25 (92.6)	
HLA-B27	Positive	2 (12.5)	1 (9.1)	1.000
	Negative	14 (87.5)	10 (90.9)	
HLA-B5	Positive	0 (0)	5 (20)	0.411
	Negative	2 (100)	20 (80)	
HLA-B51	Positive	2 (12.5)	3 (27.3)	0.370
	Negative	14 (87.5)	8 (72.7)	

HLA: Human leukocyte antigen

complicated the study of atypical meningioma.[35] Following the introduction of the three-grade classification of the WHO, studies have shown that approximately 41% of atypical cases relapse within 5 years after resection surgery, whereas only 12% of benign cases are associated with recurrence.[37] However, the treatment of choice for this tumor is still tumor resection by surgery. Considering the more invasive nature of relapsed tumor relative to primary tumor, adjuvant therapy such as radiotherapy seems to be necessary for long-term management of patients in case the resection is not complete or successful in atypical cases.[35] Previously, the interpretation of clinical manifestations and their association with tumor involvement site were an important component of the diagnostic process by the physician; however, the application of imaging technologies has facilitated the diagnosis, but no consistent screening guideline has been presented for cerebral meningiomas up to now.[2] HLAs are glycoproteins encoded by genes located on the short arm of chromosome 6.[12] This group of antigens is encoded by one of the most variable parts of the entire human genome adjacent to other genes implicated in the immune system, which has a high diversity and plays a major role in immunological processes.

There are Class I and II HLAs that play a role in antigen presentation to $CD8^+$ and $CD4^+$ T-cells, respectively. A high association has been found between HLA I and II with different diseases.[38,39] Today, some of these antigens can be used to diagnose the diseases and determine their prognosis, including type I diabetes mellitus (associated with HLA-DQ2 and HLA-DQ8), multiple sclerosis (related with HLA-DR2), systemic lupus erythematosus (linked to HLA-DR2 and HLA-DR3) as well as immune cytopathies such as ITP (associated with HLA-B8, HLA-A28, HLA-DR3, etc.).[40-44] In the meantime, studies have been conducted on the association of HLAs with glioma; for instance, there has been a relationship between HLA-G and HLA-DRB1 with glioma.[25,45] Therefore, with the aim of finding a laboratory factor for screening, diagnosis, and prognosis in meningioma patients, we investigated the expressions of HLA-B5, 7, 8, 27, and 51 whose significant relationship with various diseases has been identified.[13,21,40]

Our study is the first research evaluating the possible association between HLA-B5, 7, 8, 27, and 51 with meningioma. In this investigation, the expression of HLA-B5, 7, 8, 27, and 51 in meningioma patients was evaluated, and HLA-B5 (33.3%) was the most prevalent HLA in our studied patients, whereas the expression of other HLAs was not significant [Table 1]. The frequency of HLA-B5 in the normal Iranian population has been reported that to be 13.3%.[46] The patients under study in our research had a mean age of 54 years, and a majority of them were females, suggesting a higher incidence of meningioma in females compared to males, which is consistent with previous studies.[3,4] CBC parameters of patients were mostly normal [Table 1]. No significant relationship was observed between the expressions of HLAs with CBC parameters [Tables 2 and 3], age, sex, clinical presentations [Table 4], familial history, tumor relapse, and drug use history of patients [Tables 5 and 6] ($P > 0.05$). The higher expression of HLA-B5 (33.3%) in patients with meningioma compared to the normal Iranian population was a notable finding of our research. Our study results showed that HLA-B5 is the dominant HLA among meningioma

patients in the southwest of Iran. However, we realize that our study has its own limitations. The main limitation of our study was the sample size, which makes it difficult to conclude any definite clinical value for HLA-B5. Although this finding may suggest a correlation between meningioma and HLA-B5, further investigations are needed to achieve a definite result.

Authors' contributions

A. A. has conceived the manuscript and revised it; S. R., A. A., N. S., H. J. M., and S. M. S. P. wrote the manuscript and prepared the tables.

Research involving human participants and/or animals

All the procedures performed in the studies involving human participants were in accordance with ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR. AJUMS. REC.1397.220) as well as 1964 Helsinki Declaration.

Informed consent

Written informed consent was obtained from all patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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