Original Article

Glioma Indian scenario: Is there a human leucocyte antigen association?

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Abstract

Background: The central nervous system tumors are a rare neoplasm with little knowledge with Human Leukocyte Antigen (HLA) involvement. Primary brain tumors are cancers that originate in brain classified according to their appearance under a microscope as low grade (grade I and II) with diffuse astrocytomas, pliocytic astrocytomas, oligodendrogliomas, gangliogliomas, and mixed gliomas as common subtypes and high grade (grade III and IV). **Materials and Methods:** HLA associations in common glioma are reported from other parts of the world. The normal cancer treatment is surgery, followed by radiotherapy, and chemotherapy; nowadays immunotherapy is advised. HLA distribution in a Glioma patient was done based on serology and molecular techniques. The immune response gene studies have implicated the HLA allele association in most of the common diseases from India. Considerable variations are noted in HLA association with cancers; hence, we have summarized the HLA involvement in Glioma with respect to the literature. **Results:** HLA A*030101, A*310102, B*350101, B*4406, Cw*040101, Cw*070101, DRB1*070101, and DRB1*1001. **Conclusion:** Ethnic diversity and HLA polymorphism precipitate differential immune response genes involved in variable disease manifestations. Therefore, caste-specific HLA allelic specificity needs to be identified, which may help in early identification of the associated HLA allele and establishing clinical practices among glioma patients.

Key words: Glioma, HLA, India

INTRODUCTION

Tumors related to central nervous system (CNS) are very rare neoplasm comprising 1-2% of all malignancies.[1] A recent report on the cancer registry survey conducted by Indian Council for Medical Research on Glioma incidence in India revealed 5.8% in Mumbai, 6.7% in Bangalore, 3.5% in Chennai, 5.6% in Dibrugarh, and 28.2% in Trivandrum among males and 6.3% in Mumbai, 5.6% in Bangalore, 7.5% in Chennai, 0% in Dibrugarh, and 21.8% in Trivandrum among females.[2] Depending upon the age and clinical condition, these have differential presentation and outcomes. Among CNS neoplasm's, gliomas are the most common tumors along with astrocytomas, oligodendrogliomas, and ependymomas. Management of gliomas along with its molecular types has been reported in the literature from western countries. It is well known that geographical, genetic, and phenotypic differences in a population with regard to Human Leukocyte Antigen (HLA) can alter the response to treatment of cancers.[3]

It has been estimated in west that the chances of having glioma---a brain or spine tumor is the fastest-growing cancer known to oncologist---is about 4 in 100,000 making it a relatively rare form of cancer. Glioma is found mostly among men, often in their 70s and 80s, though it has in recent years began appearing much more frequently in 50 year olds and even younger. About 30,000 people in USA are diagnosed with glioma annually. Gliomas are ranked by cell types and in stages from 1 to 4 with stage 1 on scale published by the World Health Organization being the most benign and stage 4 the most aggressive. Stage 1 and 2 gliomas involve differentiated cells and can often be left

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untreated, or minimally treated, and have excellent survival rates, as serious cancers. Stage 3 glioma normally involves astrocytes and the disease is referred to as anaplastic asrocytoma. Stage 4 glioma is referred to as glioblastoma multiforme. The median survival for stage 3 glioma is 4 years (among UCSF patients), while prognosis for stage 4 is 12 months or less. The cell types involved are all glial cells, or non-neuronal cells that provide support and nutrition to neuronal cells. In brain, glial cells outnumber neurons by about 10:1. The main types of glial cells involved in cancer are epedymal cells, oligodendrocytes, and astrocytes. Symptoms that can include seizures, headaches, nausea, neurological, or cognitive impairment are caused by tumors infiltration of important brain centers. Symptoms depend sensitively on the location of the tumor and can vary greatly in degree. The most common treatment for glioma are surgery, both by conventional and the newer "cyberknife" procedures, radiation therapy (normally three-dimensional conformational radiotherapy) and chemotherapy with the drugs temozolomide and more recently with angiogenic blockers like bevacizumab.[4]

HLA are widely expressed cell surface molecules that present antigenic peptides to T lymphocytes and modulate the immune response against inflammatory and malignant disease.[5] Frequently tumor cells express antigen that are recognized by the immune system, where the ineffective immune response could be due to erroneous antigen presentation of HLA allele. It has also been reported that CD4+, HLA DR7-restricted T-helper lymphocytes clone recognizes an antigen shared by human malignant melanoma and glioma.[6]

The immune system is the most important biological system affected by the evolutionary pressures of diseases and is characterized by a very high level of polymorphisms. The implications of these polymorphic diversities are important in community genetics in general especially Indian caste and tribal populations, with wide variations in HLA allele repertoires. The stratified data based on the exact caste and tribal groups revealed greater diversity and genetic distances equivalent to two globally distant populations.[7] DNA-based HLA studies have further confirmed their remarkable level of allelic diversity in the Indian population. Additionally newer HLA alleles like A*0211, A*3303, A*3306, B*1405, B*2708, B*2714, DRB1*1506, DRB1*1508 have been identified to co-exist with other alleles.[8-11]

A few studies describe the varied HLA disease susceptibility in populations from the same area. Earlier studies have revealed some of the significant HLA associations with diseases among western Indians [Table 1].[7] The association of HLA B27 in ankylosing spondylitis[12] and a significantly stronger association with HLA B*2714 was identified among the Kunbi people, a major caste involved in farming from Maharashtra. HLA B12 association was observed with multiple sclerosis among Parsis and in some other western Indians.[13] The association may be attributable to a genetic phenomenon of hitchhiking, i.e. the disease spread with the migration of a community as the causative genes are linked to the HLA allele. So, the origin, migration, sympatric isolation and hence, divergence of the gene pool at HLA loci add a new dimension to community genetics with respect to a disease and its prevalence.

Table 1: HLA and disease associations observed in a western Indian population

Disease	Associated HLA	Relative risk
Leprosy	B40	3.14
Leprosy	A*1102	30
Multiple sclerosis	B12	*
Multiple sclerosis	A11,B16,Cw7	2.6,13.8,5.46
Multiple sclerosis	DRB1*15	16.15
Lymphoid leukemia	B35	*
Rh(D) isoimmunization	A3,B17,Cw2,DR4	2.60
Psoriasis	A1,B17,Cw6,	2.76,3.11,2.98,
Psoriasis	DR7,DQw3	2.15,3.16
Psoriasis	C4BQ0	10.73
Ankylosing spondylitis	B27	273.00
Ankylosing spondylitis	B27	71.50
Ankylosing spondylitis	B27	72.22
Hemophilia with synovitis	B27	34.6
Systemic lupus erythematosus	DRB*03,DQB*0302	9.67,8.02
Malaria	B49	*
HIV-1	B*3520,B*1801, Cw*1507	*
Type 1 autoimmune hepatitis	A*0222	*
ANCA-positive autoimmune disease	A*0101-B*5701	*

* Not reported. All associations were valid in the total Western Indian populations

MATERIALS AND METHODS

With the above background, a prospective review of HLA associations with Glioma reported in the literature was undertaken to compare the HLA distribution in a patient who presented with a right motor strip glioma, underwent operation, followed by radiotherapy and the anti-epileptic drug. The HLA of the patient was HLA A*030101, A*310102, B*350101, B*4406, Cw*040101, Cw*070101, DRB1*070101, and DRB1*1001 that has been earlier typed by serological (standard NIH microlymphocytotoxicity assay) and then consecutively confirmed in International Histocompatibility Workshop Serology Trays and further by molecular methods such as polymerase chain reaction

and sequence specific priming (PCR-SSP) (Dynal SSP Kits, Dynal Biotech Ltd, UK), polymerase chain reaction and sequence-specific probing (PCR-SSOP) (Dynal RELI™ SSO Kits, Dynal Biotech Ltd, UK) and polymerase chain reaction and sequence-based typing (PCR-SBT) in International Histocompatibility Workshops.

DISCUSSION

The role of HLA alleles in glioma has been reported in the literature since 1978; HLA typing of 80 glioma patients revealed a insignificant association of HLA Bw35 and DRw1.[14] Tumor biopsied cells from astrocytoma patients in culture showed expression of HLA A and HLA B antigens.[15] HLA studies from 65 glioma patients with low-grade, anaplastic or malignant astrocytic glioma (WHO grades II-IV) when compared with 157 normal asymptomatic controls from Germany have showed that HLA A*25 had a 3-fold increased risk of glioma (P=0.04), patients positive for HLA B*27, a 2.7-fold risk (P=0.03), and patients positive for HLA DRB1*15, a 2.2-fold risk (P=0.03), whereas HLA DRB1*07 was associated with a 0.4-fold decreased risk of glioma HLA DRB1*15-DRB5*51 occurrence with DRB1*11 was associated with 13.4-fold increased risk of glioma (P=0.001); hence it is concluded that single HLA antigens and their combinations along with their extended haplotypes are possibly involved in developing symptomatic cerebral glioma during their adult life.[16] Further, a study carried out on 39 glioma patients for the serum immunoglobulin estimation with B-cell phenotype markers observed a 3-4-fold increase in the IgM levels in patient's astrocytoma, which could mainly be due to a selective depletion of CD4+ cells that occurs as a reaction to tumor.[17] HLA typing of Class I and Class II preformed in 36 glioma patients from western Italy showed a positive association between HLA DRB1*14 and the presence of symptomatic cerebral glioma (OR = 2.48; P value 0.02).[6] Recently, a case control study in Sicily for HLA frequency in high grade human gliomas revealed a significant expression of HLA A*11 in patients diagnosed with high grade gliomas.[18] A prospective study from Tata Memorial Hospital on 656 patients showed that astrocytomas were the most common primary tumors. Gliomas constituted 38.7% (254 cases) of CNS tumors, with high-grade gliomas comprising 59.5% (151/254) and low grade gliomas 33.1% (79/254). Among the 19 oligodendrogliomas, 12 cases were grade II and 7 were anaplastic. Most of these tumors were seen in middle-aged men.[19]

The present analysis reveals that the heterogeneous nature of the Indian population suggesting that the population as such or even a linguistic or regional population within it cannot be considered as a panmictic pool; only a caste group may be considered as a homogeneous gene pool with its diverse haplotype combinations and high rates of consanguinity. However, it s not known how these HLA allele-dependent selection mechanisms might have influenced the disease pathogenesis among the Indian population groups. The case reported in this study belongs to Nadar, one of the prominent Dravidian caste groups of Tamil Nadu South India. Nadars are considered ancient warrior castes who were the descendants of the initial rulers of the ancient Pandian Kingdom. Earlier studies on HLA polymorphisms among Nadars have revealed a high allele frequencies of A*03011, A*31012, A*2402101, B*15011, B*3501, B*51011, Cw*02022, Cw*04011, Cw*0702, DRB1*0701, DRB1*1001, DRB1*1404, DQB1*0201 along with common unique HLA haplotypes such as A*03011-Cw*02022-B*3501, and DRB1*0701-DQB1*0201.[20,21] Future studies including KIR polymorphisms and other disease related genetic polymorphisms among different Indian caste and tribal groups would enlighten the role or epistatic interaction of HLA in disease association as well as pathogenesis in glioma.

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