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Current Understanding of Epidemiology, Genetic Etiology and Treatment of Gliomas from Indian Population

Rajib Mukherjee[1], **Tapas K Das**[1], **Kaushik Roy**[1] **and Joydeep Mukherjee**[*2]

[1]*Government Hospital, Kolkata, West Bengal, India*

[2]*Brain Tumor Research Centre, Department of Neurological Surgery, Helen Diller Family Comprehensive Cancer Centre, University of California-San Francisco (UCSF), San Francisco, CA 94158,USA*

[*]**Corresponding author:** Joydeep Mukherjee, Brain Tumor Research Centre, Helen Diller Family Comprehensive Cancer Centre, University of California-San Francisco (UCSF), HD-431, 1450, 3rd Street, San Francisco, CA 94158,USA, Tel: 415-502-7132; E-mail: joydeep.mukherjee@ucsf.edu

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Abstract

Tumors of the central nervous system (CNS) consist of 1-2% of the total cancer spectrum. Gliomas are the most common tumors within the CNS. These tumors originate from glial cells or glial precursor cells. Tumors originates from astroglial cells are known as astrocytoma, oligodendroglioma originates from oligodendroglial cells, oligo-astrocytoma are mixed tumor containing cellular property of both astrocytes and oligodendrocytes and ependymal cells gives rise to ependymoma. The World Health Organization (WHO) classification of central nervous system tumors separates glioma into four grades, in which grade I and II are defined as low grade whereas grade III and IV are classified as high grade (also known as malignant glioma). Malignant glioma includes anaplastic glioma (anaplastic oligodendroglioma, anaplastic astrocytoma, and anaplastic oligoastrocytoma) and glioblastoma. With current treatment modality, survival of patients with newly diagnosed glioblastoma is around 12–16 months. The treatment strategy includes surgery followed by adjuvant radiation and chemotherapy. From 2005, a second-generation oral alkylating agent known as Temozolomide (TMZ) became standard of care in the treatment of malignant glioma patients worldwide including India. In this current review we focused on epidemiology, molecular biology and management of gliomas emerged from India.

Key words:

Brain tumor; Glioma; Astrocytoma; Oligodendroglioma; Ependymoma; Mixed glioma- oligoastrocytoma; Epidemiology; Molecular etiology and therapeutics.

Introduction

Glioma includes tumors of all grades from astrocytoma, oligodendroglioma, ependymoma and mixed lineages. Among these malignant gliomas are most aggressive and have worst prognosis. The symptoms of glioma are cognitive change, headache and epilepsy. Moreover language disorder and progressive hemiparesis indicates tumor invasion that is characterized by edema and contrast enhancement on computed tomography or magnetic resonance neuroimaging. Unfortunately till date histological examination is considered as the gold standard after suggestive clinical and imaging features. Development of non-invasive molecular imaging is required to diagnose the tumor without performing stereotactic biopsy before or during the surgery. The median survival of grade-III glioma patient is around 3 years and grade-IV is around 12-16 months [1, 2]. Both grade-III and IV tumor grows more aggressively and invade normal brain parenchyma than lower grade ones with histologic features of nuclear atypia, increased mitotic activity and hyper-cellularity. Addition to that grade-IV tumor histologically defined by features of vascular proliferation, pleomorphic nucleus and necrosis surrounded by pseudopalisades [3]. Among all intracranial tumor, glioblastoma accounts for around 15% and almost half of all astrocytic tumors. Glioblastomas can be subdivided into primary or de novo and secondary tumors that gradually transform from lower grades. 90% of GBMs are primary glioblastoma that mostly affect the elder population. Secondary glioblastoma are more common in younger population (mean age 45 years versus 62 years) [4].

Literature on treatment of gliomas in Indian population as well as molecular diagnosis are available separately but comprehensive study / review was not found in PubMed. The need for molecular epidemiology directing the treatment of gliomas are very much require in Indian subpopulation. The present review aimed at bridging the available literature of current epidemiology, genetic etiology and treatment modality of glioma patients in India.

Epidemiological Studies on Indian Glioma Patient

In the absence of centralized cancer registration system in India, population based cancer registries representing a small population is the only option. This makes epidemiological studies incomplete and hard to even perform incase of rare CNS tumors. Moreover there is no separate registry for the adult and pediatric population. The incidence of tumor in India is 1–4/100,000 [1], it may develop at any age, and has a peak incidence in the fifth and sixth decades of life [2].

A prospective study done in 2008 from a tertiary cancer hospital documented that astrocytomas are the most common primary CNS tumors (around 39%) within a cohort of 656 patients out of which 59.5% are high-grade and 33.1% are low-grade gliomas. 19 oligodendrogliomas were found within the cohort and 7 were anaplastic and rest grade II. Most of the ependymoma presented (43.5%) were below 18 years of age. All spinal ependymoma were grade-II, whereas, eight intracranial ependymoma were of anaplastic histology. Brain stem glioma was found in 18 cases based on clinical

and radiological signs [5]. Sinha, S. et al conducted a retrospective study from 1998 to 2012 on 58 brain stem glioma patients and documented that histologically 41.4% were pilocytic astrocytoma, 34.5% were Grade II astrocytoma and 24.1% were Grade III astrocytoma [6]. In a recent report of 341 pediatric brain tumor patients, 22.87% is astrocytoma (low grade 8.5%, 12% GBM), ependymoma 9.67%, brain stem glioma 7% and oligodendroglioma 3.51% [7]. For pleomorphic xanthoastrocytoma, approximately 10individual case reports from Indian patients were found in pubmed.

Molecular studies on Indian Glioma patient

Molecular classifications of glial tumors were quite extensively performed in the last decade. Molecular studies with Indian patient samples are as follows

p53

A study conducted by Jha, P. et al. with 84 gliomas reported highest (38%) codon 72 polymorphism of arg/arg genotype [8]. Manasa, LP et al. analyzed 54 cases (33 intracranial and 21 spinal) with different grades of ependymoma (9 grade-I ependymomas, 32 grade-II ependymomas and 13 grade-III ependymomas) and found out that the mean p53 indices were higher in grade III and grade II tumors (26.26% and 26.08%) as compared to subependymomas (7.25%) [9]. Another study from Jha, P. et al. with 75 GBM patients showed 11.8% of primary adult GBM and 66.7% of secondary GBMs have TP53 mutations [10]. In 20 pediatric GBM samples, p53 protein expression was detected in 60% of the cases [11]. In 30 cases of pediatric GBM samples, p53 protein expression was observed in 63% [12] of the cases.

EGFR

In a prospective cohort of 140 adult patients diagnosed for GBM, a strong positive correlation between EGFR amplification and EGFR overexpression with p53 immuno-positivity was observed. Shorter survival was statistically associated with EGFR overexpression and increasing age [13]. Primary adult GBMs showed EGFR amplification in 37.3% and none was observed in secondary GBM (out of total 75 GBM patients) [10]. In 30 cases of pediatric GBM samples, although EGFR protein overexpression was noted in 23% of cases, corresponding amplification of the EGFR gene was rare (5.5%) [12].

CDKN2A

Sibin MK et al. analyzed 50 glioma samples for deletion of p16INK4A. Deletion of atleast one exon was observed in 20% cases. p16 gene mutation frequency was lower in Indian cohort (4.2%) [14]. In another study, out of 67 samples CDKN2A deletion was noted in 40.3% cases of GBM with majority being homozygous deletion (74%). 65.8% mutation was found in primary GBMs [15].

PTEN

Srividya MR. et al. examined for 10q23/PTEN deletion in a prospective cohorts of 73 adult patients by fluorescence in situ hybridization (FISH). Interestingly, homozygous deletion of 10q23/PTEN was frequent in patients >45 years of age and was associated with shorter survival in the entire cohort, indicating that loss of 10q23/PTEN showed clinical importance in elderly patients [16]. In a separate study 75 GBM samples were selected for molecular analysis. Primary GBM have 54.9%, secondary GBM have 33.3% and pediatric GBM had 40% PTEN deletion [10]. Immunohistochemical analysis of p53, EGFR, and PTEN in 54 cases of adult supratentorial glioblastomas demonstrated over-expression of EGFR and/or p53 emerged as significant predictors of poor outcome on multivariate analysis, despite failing to prognosticate on univariate analysis [17]. In 30 cases of pediatric GBM samples deletion of the PTEN gene was also equally rare (5.5%) [12].

IDH1/2

Agarwal S, et al. analyzed 50 diffuse glioma samples by IHC as well as DNA sequencing with 88% concordance showed 46.6% of immuno-positivity [18]. Another study with 32 gliomas of various grades and tumor subtypes, IDH1 R132H mutations was found in 18.7% tumors, while none of the cases showed IDH2 (R172G) mutations. The frequency of IDH1 mutations was higher in females (21.4%) than males (11.1%), and it was significantly higher in younger patients [19]. Sipayya V, et al. analyzed a total of 195 gliomas (30 pilocytic astrocytoma, 45 diffuse astrocytoma, 75 glioblastoma multiforme, 25 oligodendroglioma and 20 ependymoma) by immunohistochemical staining for IDH1 and 29 out of 184 (15.8%) was evaluated. 7 out of 72 GBM sample showed IDH1 mutation, of which 1 of 7 primary GBM and 6 of 7 Secondary GBM were positive for the mutation. Of all the GBMs, primary GBM showed immuno-expression in 1.5% while secondary GBM showed IDH1 expression in 85.7% cases. 42.5% of diffuse astrocytoma and 22.7% oligodendroglioma were positive for IDH1 mutation. No positive case was found in pilocytic astrocytoma and ependymoma samples [20]. Thota B, et al. performed DNA sequencing of IDH1 gene at codon 132 in 74 astrocytoma samples of different histological grades: diffuse astrocytoma, grade-II (DA), anaplastic astrocytoma, grade-III (AA), and Glioblastoma multiforme grade-IV (GBM). A total of 31 (41.9%) heterozygous IDH1 mutation was detected, of which 12 DAs (100%), 13 of 14 AAs (92.9%), and 6 of 48 GBMs (12.5%) have mutations resulting in R132H (CGT>CAT) arginine-to-histidine substitution [21]. Jha P, et al. analyzed 75 GBM cases and found that primary GBM have 11.8% IDH1 mutation and secondary GBM have 44.4% mutations [10].

MGMT

Jha P, et al. analyzed MGMT promoter methylation by methylation-specific polymerase chain reaction in 102 gliomas of various grades and subtypes. There was an inverse correlation of MGMT promoter methylation frequency with tumor grade, observed in 79.4%, 70.8%, and 56.8% of grade II, grade III, and grade IV gliomas, respectively. The difference was statistically significant in grade II *vs* IV tumors (P=036). The majority of cases with 1p/19q loss of heterozygosity also showed MGMT methylation, although the association was not significant [22]. Nehru GA, et al. analyzed DNA obtained from the frozen tissue of 27 samples of glioblastomas and three other gliomas for MGMT promoter methylation using a nested MSP assay. Sixteen samples were also subjected to bisulfite sequencing to determine the methylation status of 27 CpG sites within the sequenced region of the MGMT promoter. Data with respect to radiation, chemotherapy and survival outcome was also collected [23]. In a third study with 20 pediatric GBM cases, MGMT promoter methylation was assessed by methylation specific PCR. MGMT gene promoter methylation was observed in 50% of pediatric glioblastomas [11]. In 30 cases of childhood GBMs, MGMT promoter methylation was observed in 67% of the frozen tissues by using MSP analysis [12].

1p/19q

Suri V, et al. analyzed a small cohort of young patient and demonstrated that combined 1p/19q loss was observed in 57% and isolated 1p loss in 14% of cases [24]. A study by Sing VY, et al. demonstrated 1p and 19q co-deletions in 72.7% of grade-II oligodendrogliomas, 90.9% of anaplastic grade-III oligodendrogliomas, 22.2% of mixed grade-II oligoastrocytomas and 42.9% of the anaplastic grade-III oligoastrocytomas [25]. A third study comprising of 71 astrocytomas, that include 6 pediatric cases and rest adult cases with 20 diffuse astrocytomas, 9 anaplastic astrocytomas and 42 GBM showed that in adults, loss of heterozygosity (LOH) of 1p/19q was detected only in 50% of GBMs and 16% of diffuse astrocytomas. In pediatric GBM population, LOH of 1p or 19q was present in 50% cases [26]. Shukla B, et al. assessed 1p/19q status in 43 cases, of which 65% of oligodendroglioma (13/20) and 66.6% of mixed oligoastrocytomas (5/9) contain loss of 1p and/or 19q [27].

Molecular classification of malignant glioma is getting more and more popular in diagnosis and treatment along with classical histopathology based classification. Discovery of loss of 1p/19q heterozygosity as a major prognosticator for patients with anaplastic oligodendroglioma, being sensitive to chemotherapeutic agents and radiotherapy is a perfect example. IDH1 mutation is considered as the earliest mutation present in low-grade glioma, oligodendroglioma and secondary GBMs and is associated with favorable outcome. Amplification/overexpression of EGFR and mutation of p53 are suggestive of primary vs. secondary GBMs respectively. Discovery of several biomarkers in the last 10 years helps immensely in classify gliomas more accurately leading to better disease management and prognostication.

Treatment modality of Indian glioma patients

The treatment strategies presently available for malignant glioma in India include surgery (for removing the local lesion) followed by adjuvant radiation and chemotherapy. For the removal of gliomas in the eloquent area, awake craniotomy helps in continuous mapping of motor and language area during surgery. In one interesting study, Chako et al. underwent awake craniotomy of 84 patients for supratentorial intraaxial tumors of which 67 were glioma. On cortical stimulation, 62.6% of patients had positive localization. Neurological deficit was observed in 3 patients during tumor removal while 16 patient showed the sign at the time of wound closure, of which 7 improved to normal and 9 had mild neurological deficits at discharge. Out of these 9 patients, 4 showed mild sign of neurological deficit at a mean follow-up of 40.8 months. The surgeon get alerted by positive responses on white matter stimulation which indicate proximity of eloquent cortex and projection fibers, reducing postoperative deficits, helping the surgeon to maximally resect the tumor safely [28].

Jalali R, et al. treated 28 brain tumors patients (10 craniopharyngioma, 8 cerebellar astrocytoma, 6 optic pathway glioma and 4 cerebral low-grade glioma) with 6 weeks of stereotactic conformal radiotherapy (SCRT) of 30 fractionated dose of 54 Gy each. No change in mean full-scale IQ (FSIQ) before and after SCRT was observed at 2-year follow-up, whereas >10% decline of FSIQ was observed in one third of patients. Chances of developing a >10% drop in FSIQ was higher in younger age group (<15 compare to the older (53% *vs.* 10%, p = 0.03) [29].

Julka P, et al. conducted a study where they treated 215 GBM patients with surgery followed by radiotherapy and chemotherapy with temozolomide to study the clinical results and prognostic factors. Conventional fractionated radiation dose of 60 Gy. in 30 fractions with concomitant temozolomide (75 mg/m2/day) was employed for 6 weeks followed by another 6 cycles of adjuvant Temozolomide (150 mg/m2 for 5 days, 28 days cycle. Overall survival (OS) was found to be 44% and 18% for 1-year and 2-year respectively and median progression free survival (PFS) was 11 month. Neutropenia/thrombocytopenia was developed in 16 patients during radiation therapy. The study establishes the role of postoperative radio-chemotherapy to be the best current option for the management of GBM patients [30].

A clinical audit published from a well-known cancer centre in India was aimed at finding Temozolomide (TMZ) induced hematological toxicities. Usually grade 3-4 acute hematological toxicity is less common ranging from 10-15% with temozolomide treatment. For this study 102 adults (>18 years of age) treated with TMZ were included. Clinically significant neutropenia and thrombocytopenia was found to be 7% and 12% respectively. 7% patients needed packed-cells, growth factors, and/or platelet transfusions. Due to community-acquired pneumonia during adjuvant TMZ two patients died. TMZ induced hematological toxicity was found to be low in the patient population [31].

In one unpublished study from government hospital in West Bengal, India, 50 GBM patients were treated with higher radiation dose > 60Gy. Among them 60% patient showed progression free survival for about 16 months which is better than the conventional treatment regime of GBM, which include surgery followed by concurrent chemo-radiation with TMZ (75mg/m2 daily) and radiotherapy 60Gy in 30 fractions followed by adjuvant TMZ 150-200 mg/m2, 5 days a week, 4 weeks, for 6 cycles. The treatment plans for pilocytic astrocytoma (Gr-I) patients in the same institute are mainly surgery followed by observation with serial MRI. For grade-II astrocytoma, if the disease progress after surgery then fractionated radiation of 54Gy for 27 times is recommended. Similarly for grade-III lesion after surgery fractionated radiation of 60Gy for 30 times is recommended.

Discussion

Globally the prognosis for glioma patients is still poor in view of high recurrent rates. Resistance to radiation and chemotherapy is the main problem in the treatment of glioma and reflects multiple mechanisms, including molecular resistance to DNA damage and apoptosis, attenuation of cytotoxicity by the microenvironment, and our limited ability to deliver drugs into the brain via the blood–brain barrier. Nonetheless, chemotherapy is playing an increasingly important role in the treatment options. Currently, concomitant radio-chemotherapy with temozolomide (TMZ), an alkylating agent, is used widely in India, and has been shown to reduce the risk of recurrence and prolong patient survival. In addition to the global problem of recurrence and resistance to therapy, most of the studies originated from India were done in a single institute and in short time frame. As a result the cohort size is too small to draw a definite conclusion. Moreover epidemiology, genetic etiology, treatment and follow-up were in most cases reported separately. As a result histological biasness in diagnosis in turn governed the disease management and ultimately prognosis. There is a requirement for multi institute long-term studies of each and every type of gliomas that will include all three arms described here in this review. In conclusion, despite of single institute small-scale efforts from all over India there is urgent need of universal multicenter study protocol that include diagnosis, treatment and follow-up.

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