Original article

Analysis of brain tumors in Kashmir Valley - A 10 year study

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Abstract:

Background: Geographically Kashmir valley is isolated from the rest of the country. It has a different climate with people having different social and dietary habits. Gastric cancer, esophageal, and skin (Kangri) cancer have a higher prevalence but there is little data available on the cancers of brain. ***Objectives & Methodology:*** Aim was to study brain tumors prospectively and retrospectively, to analyse brain tumors geographically and to analyse the age and sex ratio of brain tumors in Kashmir valley. In this Retrospective and Prospective study, retrospectively (initial seven years) all patients were analyzed for their clinical symptoms, age, sex, residence, histopathologic characteristics of tumors. Prospectively (later three years) after get-ting the radiological diagnosis pathological diagnosis was arrived by procedures like open, stereotactic, and endoscopic procedures. All patients were then analysed for age, sex, residence, signs and symptoms and histopathological characteristics. Follow up was done for gliomas. Mortality and morbidity was analysed for gliomas in these 3 years. Patients who lost the follow up were considered dead. Out of 1730 patients included in our study, there were 1031 males and 699 females. The most common age group was between 41-50 years. ***Results:*** The most common tumor was gliomas followed by meningiomas. Gliomas were most common in men and meningiomas in females. Out of all the histological grades in gliomas, the glioblastoma multiforme (GBM) was the most common, and frontal lobe was the commonest anatomical site involved. The most common symptom in our study was headache followed by vomiting.

Key words: Kashmir vally; brain tumors; analysis; outcome

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Introduction:

The term ''brain tumors'' refers to a mixed group of neoplasms originating from intracranial tissues and the meninges with degrees of malignancy ranging from benign to aggressive. Each type of tumour has its own biology, treatment, and prognosis and each is likely to be caused by different risk factors. Even 'benign'' tumors can be lethal due to their site in the brain, their ability to infiltrate locally, and their propensity to transform to malignancy[1]

The incidence of brain tumors has increased over

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time and differs according to gender, age, race and ethnicity, and geography. Based on nine geographic areas surveyed by the United States SEER program since 1973, the age-adjusted incidence rate for malignant brain tumors has increased among men[3] Most, if not all, of this increase probably is attributable to improvements in diagnostic imaging (eg, use of CT and MRI), increased availability of medical care and neurosurgeons, changing approaches in the treatment of older patients, and changes in classifications of specific histologies of brain tumors[4-6]. For all central nervous system (CNS) tumors, of which brain tumors are the majority, the age-adjusted average annual (1998 to 2002) incidence rate for women (15.1 per 100,000 person years) is slightly greater than that for men (14.5 per 100,000 person years)[2]

Gliomas are approximately twice as common among whites as compared to blacks, as are germ cell tumors. There are no well-described explanations for the observed race and ethnicity differences; however, genetic differences may contribute to race-related incidence differences. Brain tumor incidence rates vary moderately by geographic region in areas that report to CBTRUS[2].

There is worldwide geographic variation in the incidence of brain tumors; for example, malignant brain tumors occur in Japan with less than half the frequency of that in Northern Europe. India have an incidence approximately one fourth that of the high-incidence countries[6,8]. The relative 2-year and 5-year survival probabilities associated with primary malignant brain tumors diagnosed between 1998 and 2003 are 37.7% and 30.2%, respectively[3]. Although the prognosis is poor for many patients who have malignant brain tumors, 2-year survival probability for patients who have malignant brain tumors has increased from 28.5% in 1975 to 38.7% in 2002[3].

Some meningioma tumors express progesterone receptors, and this expression occurs to a greater degree in women[10-13]. Exposure to therapeutic doses of ionizing radiation is the only established potentially modifiable brain tumor risk factor[6,14]. Children irradiated for treatment of tinea capitis also have a greater risk for pituitary adenoma[15].

Several environmental and behavioral risk factors like head injury and trauma (for intravascular brain tumors)[16], head injury and trauma (for nonintravascular brain tumors)[6,16-20], dietary calcium intake (for glioma)[20,21], dietary N-nitroso compound intake (for glioma and meningioma)[23-26], dietary antioxidant intake (for glioma)[22-25], dietary maternal N-nitroso compound intake (for childhood brain tumors)[6,20], dietary maternal and early life antioxidant intake (for childhood brain tumors), maternal folate supplementation (for primitive neuroectodermal tumors)[20,27], tobacco smoking (for glioma and meningioma)[20,24,28] alcohol consumption (for glioma, meningioma, and childhood brain tumors)[14,29], may also be responsible.

Grossman and colleagues[30] showed that brain tumors occur in families with no known predisposing hereditary disease and that the pattern of occurrence in many families suggests environmental causes. There is strong epidemiologic evidence that genetic factors are associated with brain tumor risk[6,31]. Persuasive evidence has accumulated over the past decade that immunologic factors related to allergy, allergic conditions, and infections have an impact on glioma and glioblastoma risk. Reduced glioma or glioblastoma risk has been attributed to allergy and allergic conditions[32-38], autoimmune diseases[32,38], reported history of varicella-zoster virus (VZV) infections, and positive IgG to VZV[39-41].

Material and methods:

The study was carried out at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, which is a 750 bedded single tertiary care hospital catering to the entire population of Kashmir valley. From 1st January 2000 to December 2009, all the brain tumor patients who were admitted in SKIMS were studied. The study was carried out in two phases, Retrospective and Prospective. Retrospective study was done from January 2001 to December 2007 and patients files were reviewed from medical records department and with help from the Department of Pathology and Department of Radiation oncology SKIMS. All such patients were then retrospectively analyzed for their clinical symptoms, age, sex, residence, histopathologic characteristics.

Prospectively patients from January 2008 to 1st December 2009 were analysed, all base line investigations were done and patients were subjected to various radiological imaging as was necessary to diagnose such cases. Final diagnosis was arrived by way of any of procedures like open, stereotactic, and endoscopic procedures. The attendants of such patients who lost to follow up or died or refused surgery were informed through media to present themselves with all the records of such patients, these patients were also recorded. All patients were then analysed for age, sex, residence, signs and symptoms and histopathological characteristics. Follow up was done for gliomas, which is the most common primary malignant brain tumor for 3 years (January2007-December2009).Mortality and morbidity was analysed for gliomas in these 3 years. Patients who lost the follow up were considered dead. Ethical approval was taken prior the study from Sher-i-Kashmir Institute of Medical Sciences (SKIMS)

Results:

From January 2001 to December 2009 a total of 1834 patients of brain tumors were seen out of which 1730 had histologically confirmed brain tumor, so only 1730 patients of brain tumor were included in our study rest 104 patients were not included in our study. Out of 1730 patients there were 1031 males and 699 females. (Fig 1)

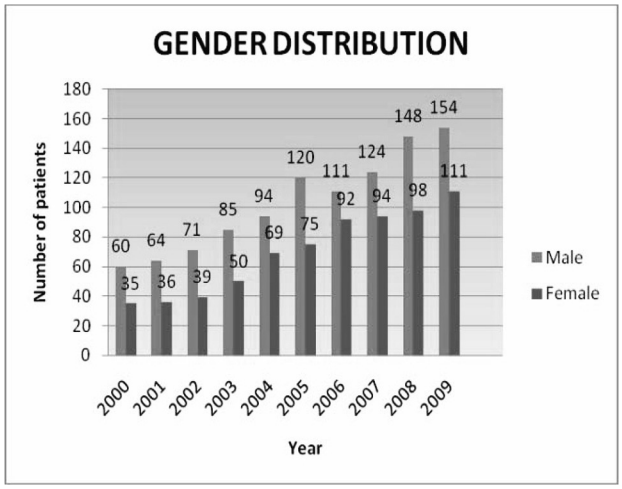

Fig 1: Bar chart showing gender distribution.

the most common age group involved in our study was between age group of 41-50 years.

Fig 2)

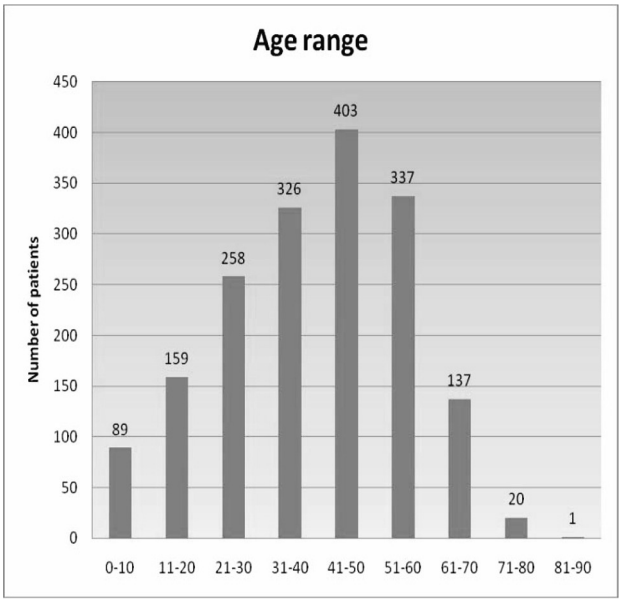

Fig 2:Bar chart showing the age distribution in brain tumor patients.

The most common tumor was gliomas followed by meningiomas (Fig 3)

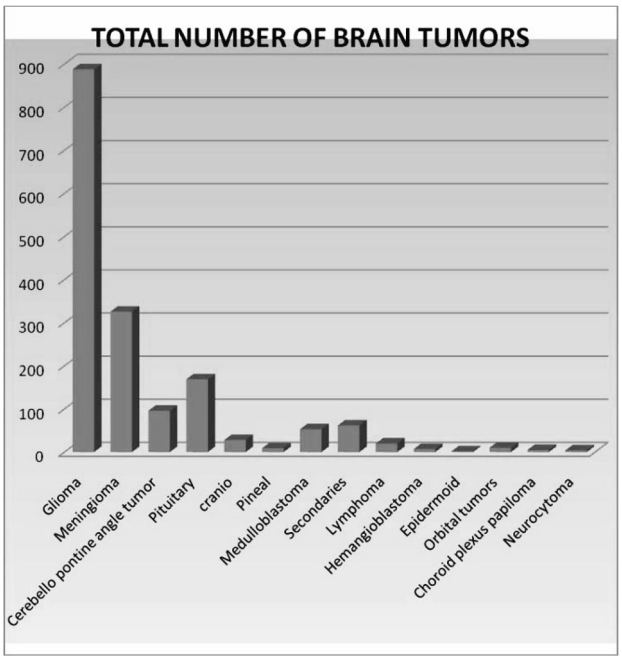

Fig 3: Bar chart showing different types of tumors in Kashmir.

and gliomas were most common in men and meningiomas in females. Out of all the histological grades in gliomas, the glioblastoma multiforme (GBM) was the most common grade found in 49.5% patients, (Fig 4)

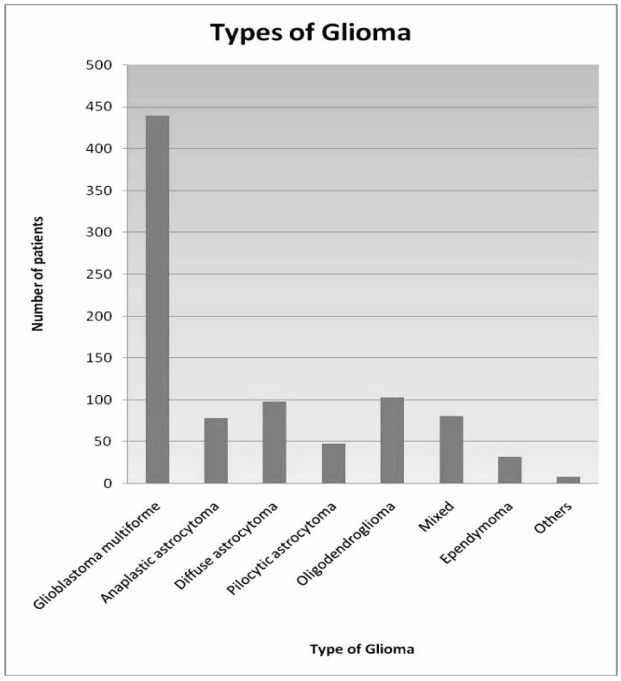

Fig 4: Bar chart showing types of gliomas.

and frontal lobe was the commonest anatomical site involved. (Fig 5)

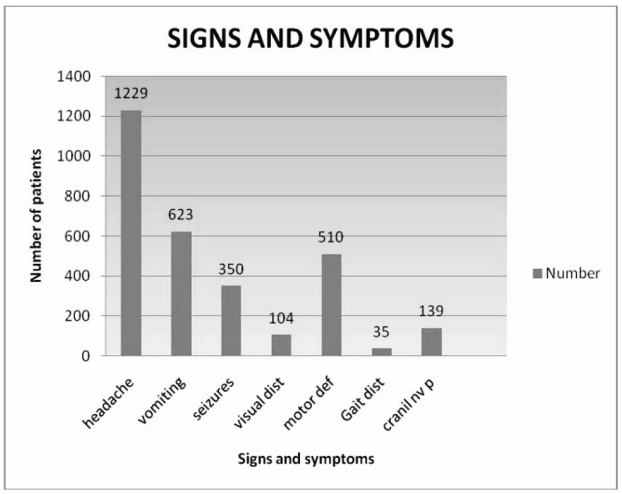

Fig 5: Bar chart showing signs and symptoms.

The most common symptom (Fig 5) in our study was headache (71.0%) followed by vomiting (36.0%).

Discussion:

Brain tumors appear to show an increasing trend over the past 30 years, but the rise probably results mostly from use of new neuroimaging techniques. Treatments have not improved prognosis for the most rapidly fatal brain tumors. Established brain tumor risk factors (exposure to therapeutic ionizing radiation, rare mutations of parental genes, and familial history) explain only a small proportion of brain tumors, and only one of these potentially is modifiable. It is likely that genetic and environmental characteristics play a role in familial aggregation of glioma, and these factors have not been identified. Among associations currently being investigated, those of interest include reproductive and menstrual factors for glioma and meningioma, cell phone use for glioma and acoustic neuroma, familial aggregation of meningioma, allergic conditions for glioma, and a variety of inherited polymorphisms potentially associated with glioma.

Current research on glioma and polymorphisms associated with allergic conditions and immunologic responses may aid in understanding the complex immunologic modulation of gliomagenesis. Focused a prior hypotheses will be needed for these studies and for studies involving genetic polymorphisms that, in conjunction with environmental carcinogens or behavioral factors, may increase brain tumor risk. In addition to these promising leads, new hypotheses should consider previous findings from well-established risk factors, such as gender, race, and ethnicity. New concepts in brain tumor etiology and clinical management are the goal of such research, with an aim at eradicating this devastating disease.

Kashmir valley is different from rest of India geographically. It has a different climatic and physical environment and different social and dietary habits. Its population is 5.5 million. Muslims constitute more than 90% of its population[79]. This study provides an insight into the demographic features of the brain tumors in a population, which has a distinct culture, social and dietary habits and has a climate, which is distinct from rest of India.

Various studies have been undertaken to study the epidemiology of brain tumors in different parts of world and we took a study to analyse brain tumors geographically, to study age patterns, sex ratio and the types of brain tumors for 10 years. Mortality and morbidity of gliomas was analysed for a period of 3 years (2007,2008 and 2009). In our study malignant brain tumors were more common in males and non-malignant brain tumors more common in females which is in accordance with most of studies in literature[1,45,50,67]. This difference might reflect real and important differences in the aetiology or natural history of the disease in both men and women. Men usually interact with medical care system more often than females and more frequent visits to a health

care system, more chances of detection of tumor.

Gliomas were most common in men and meningiomas more common in females as observed by most authors[74,48]. High grade gliomas were most common in our study (25.4%) and meningioma was next most common tumor(18.8) which is slightly lesser than that observed by Melissa et al[74] who found (30.5%) and (29.4%) for high grade gliomas and meningiomas respectively. Among gliomas glioblastoma multiforme was most common (49.5%) followed by diffuse and anaplastic astrocytoma which is nearly same as seen in literature[73,43,48,71] In accordance with previous studies, we found that very young adults have the lowest risk of brain cancer and that the risk continues to rise with age. Higher incidence for those in older age groups suggests a possible role for bioaccumulation from environmental toxic exposure in the cause of malignant brain tumor.

Our results also confirm previous observations of a higher incidence of brain cancer in men compared with women. Although some investigators have suggested that female sex hormones have a protective effect against brain cancer, others have suggested innate differences in the susceptibility of X and Y chromosomes to tumorgenic stimuli. In gliomas the most common age group involved was 41-50 years which is younger than that seen in literature[74,48]. Male female ratio in our study for gliomas is 2:1 as compared to other studies Miguel et al[48] 1.8:1 and Agnes et al[43] 1.59:1.

The nonuniform anatomic distribution of gliomas with frontal and temporal predominance may reflect the involvement of developmental, neurochemical, or functional factors in the pathogenesis of gliomas. In one study, allelic loss was most common in oligodendrogliomas located in the same anatomic areas (frontal lobe) where we found the highest tumor frequency[75,76]. It has also been suggested that tumors in different parts of the brain arise from different precursor cells or that differences in the extracellular environment may account for the differences between lobes[77]. Furthermore, involvement of structural and functional differences between brain regions, including energy metabolism, architectonic tissue arrangements, and interaction between neuronal and glial cells, has been postulated.

In our study anatomical location is frontal (36%), temporal (27%), occipital (3.4%), cerebellum (1.6%), brain stem (4.5%) which is approximately same as described by Larjavaara et al[72] who found gliomas in frontal lobe (40%), temporal (25%), parietal (14%), brainstem (4.1). Helle collatz[55] et al also found same location of gliomas. Gliomas were located more common on right side than left side while meningiomas were seen more on left side as was seen in literature[72]. Right side was involved in 55% and left side in 36% of patients in our study.

Sellar tumors were more common in females in our study and most common age involved was 41-50 years which has been also proved by other studies[49]. Pituitary tumors accounted for 9.7% of total tumors which is nearly same as seen in literature[55,68]. Cerebello pontine angle tumors were more common on right side and meningiomas were more common on left side, similar findings were seen by Inskip et al[60]. Brain tumors were seen most commonly in urban areas as compared to rural areas as was seen by Sandeep Doera et al[68]. Although farming and pesticide exposure have been suggested as potential risk factors, either their effects are small or there are larger risk factors operating in urban areas. Differences in access to medical care may also be a reason for this discrepancy between urban and rural incidence rates.

The most common symptom in our study was headache (71%), followed by vomiting (36%) and motor deficits (29.4%). Seizures were seen in nearly 20.2% of all tumors but were more common in low grade glioma. In an analysis on epileptogenic brain tumors in Kashmir, the overall frequency of seizure in brain tumors was 29% with oligodendrogliomas as the most epileptogenic tumors[78]. Out of 326 patients, 14 underwent stereotactic biopsy, which revealed low-grade gliomas in 9 and high grade gliomas in 5 patients and these 9 patients were later subjected to radiotherapy because of their deep-seated location. Surgical decompression was performed in 312 patients, 122 were confirmed on biopsy as low-grade gliomas and 190 were as high-grade gliomas. Re exploration was carried out in 5 and 12 patients of low and high-grade gliomas, respectively, because of immediate postoperative complication (mostly hematomas).

Five patients on follow-up developed bone flap osteomyelitis, which had to be removed and later

cranioplasty was carried out. Nine patients had hydrocephalus and all underwent cerebrospinal fluid diversion before resection of the tumor. Revision surgery at follow-up for recurrence was done in 12 and 21 patients of low and high-grade gliomas, respectively. Patients with high-grade gliomas were followed with postoperative radiotherapy and chemotherapy. The mortality in low-grade gliomas was nil and 7 patients of high-grade glioma died in immediate postoperative period. The follow-up for gliomas varied from 6 months to 3 years. A total of 33 patients had recurrence of the tumor after first surgery. All other patients of low-grade glioma are on a regular follow-up.

Out of 153 patients of GBM 8 had to be reoperated within an average period of 7 months (range 6-11 months).Out of 153 patients 109 died (these included those 20 patients who lost to follow up) and remaining are on follow up.12 patients survived more than 2 years. All the patients of recurrence died within 7 months of re surgery and radiotherapy. We prefer resection in all cases of gliomas unless the tumors are deep seated or involving eloquent areas. In his study, on low-grade gliomas Hoffman et al[91] concluded that resection should be considered in all patients both at presentation and recurrence. Our experience with low-grade gliomas shows that with an aggressive surgical management, most patients do well as of a total of 122 patients, 12 had recurrence. For low-grade gliomas, we favour an aggressive resection. Most of the studies favour aggressive resection for low-grade gliomas, whereas other authors are of the view that extensive resection does not affect the patient survival or tumor progression[80-82].Though some authors recommend radiotherapy for low-grade gliomas after the initial resection but most have noted that radiation therapy did not offer more benefit[83]. Patients with high-grade gliomas were followed with postoperative radiotherapy and chemotherapy.

The standard therapy for malignant gliomas involves surgical resection and when feasible, radiotherapy and chemotherapy[84,85]. Malignant gliomas cannot be eliminated completely surgically because of their infiltrative nature but patients should undergo maximum surgical resection whenever possible. Patients with extensive resection have a modest survival advantage[86-88]. The addition of radiotherapy to surgery increases survival among patients with glioblastoma from a range of 3 to 4 months to a range of 7 to 12 months[89-90]. Five year survival is rare in GBM and is reported to be 4% to 5% only[76]. We had 12 patients of GBM who survived for 2 years and it remains to be seen if they belong to a subset of GBM with a favourable outcome/long term survival. Addition of chemotherapeutic agents, targeted molecular agents and antiangiogenic agents may enhance the effectiveness of radiotherapy[90]. Stereotactic biopsy was carried out in 14 cases, of which 5 were high-grade gliomas, which were later subjected to radiotherapy because of their deep seated location. Stereotactic biopsy is preferred only in patients who have inoperable tumors that are located in critical areas[85]. Our experience with low-grade and high-grade gliomas shows that glioma pattern and its demography does not vary considerably when the data from a tertiary care center in a culturally and geographically distinct area (Kashmir) is analyzed. In contrast the tumors of esophagus, stomach, colorectum, and skin have a higher prevalence in the valley and exhibit a pattern, which is distinct so far as the demographic and clinical features are concerned[75].

Conclusion:

The distinctive features of our study were:

Malignant brain tumors were more common in males and non- malignant brain tumors more common in females.

The most common symptom in our study was headache followed by vomiting.

Gliomas were most common in men and meningiomas more common in females. High grade gliomas were most common in our study and meningioma was next most common tumors. Low grade gliomas did well with aggressive surgical management.

In gliomas the most common age group involved was 41-50 years. Male female ratio in our study for gliomas was 2:1.

Among gliomas glioblastoma multiforme was most common followed by diffuse and anaplastic astrocytoma .

Glioma were commonest in frontal lobe followed by temporal lobe. Gliomos were located more common on right side than left side while meningiomas were seen more on left side.

Brain tumors were seen most commonly in urban areas as compared to rural areas.

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