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Original Research Paper

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EPIDEMIOLOGY, IMAGING, DIAGNOSIS, CLINICAL PRESENTATIONS AND TREATMENT OF PRIMARY GLIOBLASTOMA IN RELATION TO PROGNOSIS: A CLINICAL CASE STUDY

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ABSTRACT GBM is the most common primary intracranial malignancy. Previous studies found its incidence varying substantially by age, sex, race and ethnicity and survival also varies by country, ethnicity and treatment. There is slight predominance in males, incidence increases with age. The standard approach of therapy is the newly diagnosed setting include surgery followed by concurrent radiotherapy with temozolomide. The recently revised classification of GBM is based on molecular profiling notably isocitrate dehydrogenase mutation status. Our study included only patients who had undergone surgery in our institute in the past 1 year and diagnosed with grade IV astrocytoma as per biopsy report. We have excluded patients with other high grade tumors. We have used non-invasive brain imaging techniques such as CT scan and MRI for visualising tumors. We have included 32 patients, 22 men and 10 women, who were diagnosed with glioblastoma in our institute in the past 1 year . The median age of diagnosis among men is 50 years and that of women is 46 years. All of our patients were from Eastern India. Among these, 8 men and 2 women expired within 3 months of undergoing surgery before radiotherapy and chemotherapy. Thus, the mortality rate was nearly 31% during our study. We have found most of the patients presenting with headache, nausea, vomiting, seizure and hemiparesis. Extent of resection has varied from patient to patient thus leading to differences in outcome, morbidity and mortality. Outcome depends on performance status, advanced age, eloquent location, extent of resection and availability of chemo-radiotherapy.

KEYWORDS : Primary glioblastoma, astrocytoma, brain tumour

INTRAODUCTION:-

Glioblastoma or Glioblastoma Multiforme (GBM) is one of the deadliest human cancer (1). It is the synonym of grade IV astrocytoma according to World Health Organization classification . It is the most predominant and aggressive primary brain tumor, which affects mainly adults (2). It has an extremely poor prognosis (3). Management consists of surgery, followed by radiotherapy and chemotherapy (4). Previous studies found its incidence varying substantially by age, sex, race and ethnicity and survival also varies by country, ethnicity and treatment. There is slight predominance in males, incidence increases with age. In this study, 32 patients with this disease underwent treatment in our institute in the past 1 year.

The disease incidence was significantly high in males in our study- comprising of about 69% of our patients. The location of glioblastoma in our study include parts of telencephalon like frontal lobe, parietal lobe, temporal lobe, occipital lobe, corpus callosum and hippocampus, parts of diencephalon such as thalamus, mesencephalon and parts of metencephalon like pons. Epithalamus, metathalamus, subthalamus, hypothalamus, hypophysis cerebri, cerebellum and medulla oblongata were unaffected in the patients of our study. Clinical manifestations in these patients were found to be headache, blurred vision in one eye, hemiparesis, dysphasia, aphasia, receptive sensory aphasia, dysarthria, nausea, vomiting, seizures, altered sensorium, hypomnesia, neck pain, incontinence of urine and faeces, anger issues, loss of appetite and consciousness. Mortality rate during our study was nearly 31%.

METHODOLOGY:-

Our study included only patients who had undergone surgery in our institute in the past 1 year and diagnosed with grade IV astrocytoma as per biopsy report. We have excluded patients with other high grade tumors. The relevant data was tabulated and percentage values calculated in this observational study. Parameters used are as follows :

EPIDEMIOLOGY:-

We have included 32 patients, 22 men and 10 women, who were diagnosed with glioblastoma in our institute in the past 1 year . The median age of diagnosis among men is 50 years and that of women is 46 years. All of our patients were from Eastern India.

IMAGING:-

We have used non-invasive brain imaging techniques such as CT scan and MRI for visualising tumors. MRI is the gold standard imaging technique due to their superior soft tissue contrast, which allows the complexity and the heterogeneity of the tumor lesion to be better visualized than a CT scan. Hypointense lesions are seen on T1- weighted MRI, whereas hyperintense lesions are visualised on proton density weighted and T2-weighted images. Glioblastomas show a central area of necrosis surrounded by white matter edema (5) (Figure 1).

DIAGNOSIS:-

A high- grade glioma is suspected through MRI images. The diagnosis- grade IV astrocytoma is confirmed by HPE of the tumor samples. 2 of our female patients have been diagnosed with gliosarcoma, which consists of both gliomatous and sarcomatous components and the other 30 patients were diagnosed with glioblastoma, which is composed of only gliomatous components (6).

PATHOGENESIS- SITE OF OCCURRENCE:

The site of lesion of patients in our study include parts of prosencephalon, mesencephalon as well as rhombencephalon. The location of this tumor among our subjects were parts of telencephalon, diencephalon, mesencephalon and metencephalon . None of the patients developed this tumor in epithalamus, metathalamus, subthalamus, hypothalamus, cerebellum and myelencephalon. 4 of our patients developed butterfly glioblastoma involving both cerebral hemispheres. 16 of our patients developed GBM only on left hemisphere of brain and

another 12 patients developed GBM only on right hemisphere of brain, 2 of them on hippocampus, 2 of them on thalamus, 2 of them on midbrain and 2 of them on pons. 28 of our patients developed lesion only on cerebrum. The most common areas of GBM among our patients were parietal, temporal and frontal lobes and corpus callosum of cerebrum. Other areas of GBM among our patients include occipital lobe, thalamus, hippocampus, midbrain and pons. Few distinct areas of lesion in cerebrum were periventricular region, pericallosal region, perisylvian region, basal ganglia and Wernicke's area.

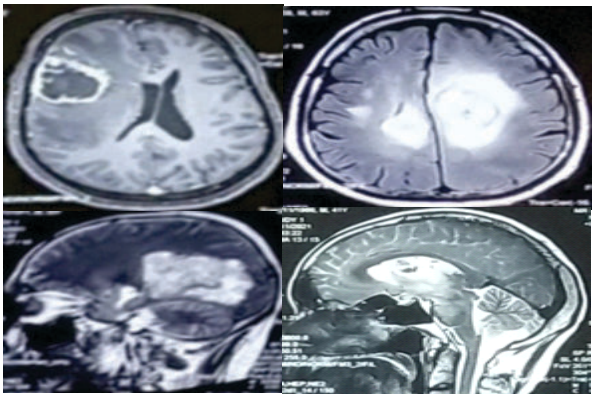

Figure 1- MRI images of 4 different GBM patients. A) Axial view- Gliosarcoma involving lesion in right frontal lobe, B) Axial view- Butterfly glioblastoma involving lesion in left fronto-parietal, thalamic and periventricular white matter, corpus callosum, basal ganglia and right parietal lobe. C) Left sagittal view- Lesion in parieto-temporo-occipital lobes. D) Left sagittal view- Lesion in parieto-temporal lobes, periventricular region, midbrain and pons.

HISTOPATHOLOGICAL FEATURES:

The histopathological findings in our tissue samples showed glial tissue with increased cellularity and pleomorphism, atypical mitotic activity, large areas of necrosis and microvascular proliferation. Several gemistocytes were seen is certain samples. A few bizarre tumor giant cells were also seen in few samples. Hyperchromatic astrocytes were arranged dispersely in fibrillary background in some samples. Pseudo palisading arrangement of tumor cells were noted in few samples. Accentuation of blood vessel with glomeruloid body with areas of haemorrhage were also found. Tumor cells with severe nuclear atypia, spindle shaped in the form of intersecting fascicles, inconspicuous nucleolus in a focally necrotic glial stroma and calcification of glomeruloid body were also observed in certain samples.

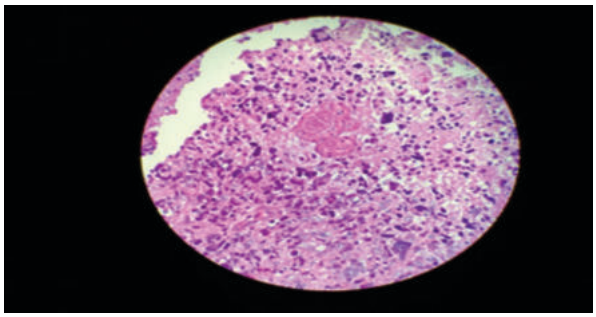

Figure 2: Histopathological features of GBM

Clinical presentations:-

Our patients had reported with a variety of clinical presentations. The most common symptoms were headache, nausea, vomiting, hemiparesis and seizures. The other symptoms were altered sensorium, blurred vision in one eye, neck pain, sensory aphasia, motor aphasia, dysphagia, dysarthria, hypomnesia, loss of consciousness and appetite , incontinence of urine and faeces and anger issues.

Sl. No	Area of lesion	Clinical presentations
1	Right cerebral hemisphere	Left-sided hemiparesis
2	Left cerebral hemisphere	Right-sided hemiparesis
3	Perisylvian region	Aphasia
4	Wernicke's Area	Sensory aphasia
5	Cortex	Convulsion
6	Brainstem	Altered sensorium, cranial nerve palsy.
7	Lobar	Memory loss, loss of planning, aggresion, rage

Table 1. Correlation between area of lesion and clinical presentations

Figure 3. Disease incidence and mortality among glioblastoma patients

Among these, 8 men and 2 women expired within 3 months of undergoing surgery before radiotherapy and chemotherapy. Thus, the mortality rate was nearly 31% during our study. 2 of our male patients reported recurrence of GBM within 7 months of undergoing surgery.

Table 2 : Extent of resection of tumors (EOR)

EOR	Number	%
Gross total resection	25	78.12
Near total resection	3	9.37
Subtotal resection	2	6.25
Biopsy	2	6.25

Post-surgery Complications:

Few symptoms vanish after surgery whereas few symptoms stay; few symptoms may increase and some new symptoms may arise post surgery. It is clearly demonstrated in the following table below:

Table 2: Post operative complications

Complications	Number	%
Headache	25	78.12
Increased hemiparesis	7	21.88
Uncontrolled seizures	3	9.37
Visual disturbances	4	12.5
Language difficulty	7	21.88
Memory deficit	9	28.12
Altered sensorium	5	15.62
Bowel and bladder incontinence	4	12.5
Recurrence	2	6.25

DISCUSSION:-

Glioblastoma is the most common primary malignant brain tumour in adults. Given its poor prognosis, treatment and determination of EOR to enhance overall survival continues to be a greatly researched topic. At this time, the mainstay of treatment for newly diagnosed glioblastoma is microsurgical resection with additional radiation therapy and chemotherapy. The surgical approach must be individualized for each patient. A fine balance must ensue to minimize morbidity while maximizing quality of life and extending survival.

Awake craniotomy is performed when a glioma is located near eloquent cortex in areas that includes, but not limited to, the precentral gyrus (motor strip), corticospinal tracts, Broca's speech area, Wernicke's speech area, and the brainstem. This technique can be of value for lesions that are on the surface to determine which portions of the tumor are resectable as well as deep seated tumors to determine a safe trajectory to the lesion. There are multiple limitations in performing an awake craniotomy (7). Patients cannot be claustrophobic, have psychiatric issues such as anxiety, or neurocognitive issues such as dementia or mental retardation.

The majority of glioma surgery entails a standard craniotomy approach with the patient under general anesthesia. Prior to intra-operative navigation, craniometrics were used and larger incisions/craniotomies were created to have adequate exposure (8). Currently with the use of intra-operative navigation systems, the surgeon can precisely determine the tumor location and plan the incision and craniotomy accordingly (9). This helps decrease operative time, limit the size of the incision and craniotomy, and it can also help determine the extent of resection (EOR) in relation to nearby critical structures.

In one of the largest studies to date that included 500 newly diagnosed glioblastoma patients, Sanai and colleagues from University of California, San Francisco, demonstrated that an EOR as low as 78% is associated with improved overall survival. Step-wise improvement in overall survival was shown beyond these margins and even at the highest levels of resection, all together suggesting the utility of both sub-total and gross-total resection in the treatment of newly diagnosed glioblastomas (10).

GBM is primarily diagnosed at older age with a median age of 64 at diagnosis (11,12). Th incidence increases with age peaking at 75-84 years and drops after 85 years (11). The age at diagnosis tends to be higher fro primary GBM (mean age of 55 and median age of 64) than for secondary GBM (mean age of 40 years) (13). GBM is uncommon in children (11). In our study, the median age of diagnosis among men was 50 years and that of women was 46 years.

In this study , the pie charts revealed the disease incidence to be 69% in males and 31% in females. The disease mortality charting revealed 80% in males and 20% in females.

GBM is most commonly located in the supratentorial region (frontal, parietal, temporal, occipital lobes) with the highest incidence in frontal lobes, multiple lobes (overlapping tumors) followed by temporal and parietal lobes. GBM is rarely located in the cerebellum, very rare in the spinal cord (12, 14, 15, 16).In our study, most common areas of GBM were parietal lobe, frontal lobe, temporal lobe and corpus callosum .

HP features revealed glial tissue with increased cellularity and pleomorphism, atypical mitotic activities and large areas of necrosis and microvascular proliferation. Our patients presented most commonly with headache, nausea, vomiting, hemiparesis and seizures. Post surgery, hemiparesis aggravated in some, hemiplegia developed in some, aphasia, dysphasia and dysarthria in some.

Due to its high degree of invasiveness, radical tumor resection is not curative. There is experimental evidence that GBM contains a subpopulation of highly tumorigenic cells (GBM stem cells) from which recurrent GBM is thought to derive (17-19), and that GBM has the capacity to differentiate into multiple lineages of tumor genesis(17,19,20). Primary GBM occurs de novo without evidence of a less malignant precursor whereas secondary GBM develops from initially low grade diffuse astrocytoma or anaplastic astrocytoma.

Factors associated with risk of GBM are previous radiation, decreased susceptibility to allergy, immune factors and immune genes, and some nucleotide polymorphisms, detected by genome -wide association (21,22). There is no substantial evidence of GBM association with lifestyle characteristics , such as cigarette smoking, alcohol consumption, drug use, or dietary exposure to nitrous compounds (23). Some reports have mentioned its association with mobile phones(24, 25). Prognostic factors that affect the survival of GBM patients include the respectability of the tumor, its location size, multifocality, as well as advanced age, comorbidities, and the patient's general condition (26).

Surgery enables a histological confirmation of the clinical diagnosis and also has decompressive and cytoreductive effects, with an advantage of increased survival with complete resection (27). Tumor fluorescence derived from 5-aminolevulinic acid enabled a more complete resection of contrast-enhancing tumor, leading to improved progression-free-survival in patients with GBM (27). The main contra-indications to resective surgery are poor performance status (Karnofsky of less than 70), advanced age, and eloquent location (13). The combination of radio-therapy and TMZ chemotherapy is the most effective adjuvant therapy shown to prolong survival following primary resection. Radiotherapy followed by TMZ results in significantly prolonged survival compared with radiotherapy alone (28). Treatment of GBM remains challenging. The current experience in GBM treatment shows that several targets should be approached. Therefore, rational combinations between established treatments and new approaches aiming, for example, at inhibition of angiogenesis, induction of apoptosis, or inhibition of several signal transduction pathways might offer the best opportunity to improve prognosis.

CONCLUSION:-

GBM is still the most malignant primary brain tumour with clear predominance in males. The multimodality approach to glioblastoma remains the cornerstone of the therapeutic approach in the newly diagnosed setting. Surgical resection , radiochemotherapy combined with improved supportive and palliative care to not only improve survival outcomes but also to enhance the quality of life for both patients and caregivers. However, resent advances in genetic and molecular research is also going on.

Conflict of interest:-
The authors have no conflicts of interest. No financial support was present.

ABBREVIATIONS :-

GBM - Glioblastoma multiforme
HPE- Histopathological examination
TMZ- Temozolomide
CT- Computed Tomography
MRI- Magnetic Resonance Imaging
EOR- Extent of resection of tumors

REFERENCES:-

1. Noch EK, Ramakrishna R, Magge R. Challenges in the Treatment of

Glioblastoma: Multisystem Mechanisms of Therapeutic Resistance. World Neurosurg. 2018 Aug;116:505-517. doi: 10.1016/j.wneu.2018.04.022. PMID: 30049045.
2. Wirsching HG, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol. 2016;134:381-97. doi: 10.1016/B978-0-12-802997-8.00023-2. PMID: 26948367.
3. Choi BD, Maus MV, June CH, Sampson JH. Immunotherapy for Glioblastoma: Adoptive T-cell Strategies. Clin Cancer Res. 2019 Apr 1;25(7):2042-2048. doi: 10.1158/1078-0432.CCR-18-1625. Epub 2018 Nov 16. PMID: 30446589; PMCID: PMC6445734.
4. Maggs L, Cattaneo G, Dal AE, Moghaddam AS, Ferrone S. CAR T Cell-Based Immunotherapy for the Treatment of Glioblastoma. Front Neurosci. 2021 May 25;15:662064. doi: 10.3389/fnins.2021.662064. PMID: 34113233; PMCID: PMC8185049.
5. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. Asian Pac J Cancer Prev. 2017 Jan 1;18(1):3-9. doi: 10.22034/APJCP.2017.18.1.3. PMID: 28239999; PMCID: PMC55631
6. Barresi V, Cerasoli S, Morigi F, Cremonini AM, Volpini M, Tuccari G. Gliosarcoma with features of osteoblastic osteosarcoma: a review. Arch Pathol Lab Med. 2006 Aug;130(8):1208-11. doi: 10.5858/2006-130-1208-GWFOOO. PMID: 16879025.
7. Meyer FB, Bates LM, Goerss SJ, et al. Awake craniotomy for aggressive resection of primary gliomas located in eloquent brain. Mayo Clin Proc 2001;76:677-87. [PubMed]
8. Ciric I, Ammirati M, Vick N, et al. Supratentorial gliomas: surgical considerations and immediate postoperative results. Gross total resection versus partial resection. Neurosurgery 1987;21:21-6. [PubMed]
9. Romano A, D'Andrea G, Minniti G, et al. Pre-surgical planning and MR-tractography utility in brain tumour resection. Eur Radiol 2009;19:2798-808. [PubMed]
10. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115:3-8. [PubMed]
11. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro Oncol. 2013;15(Suppl):2ii–56.
12. Chakrabarti I, Cockburn M, Cozen W, Wang YP, Preston-Martin S. A population-based description of glioblastoma multiforme in Los Angeles County, 1974–1999. Cancer. 2005;104:2798–06. http://dx.doi.org/10.1002/cncr.21539
13. Taylor A, Karajannis MA, Harter DH. Glioblastoma multiforme: State of art and future therapeutics. Surg Neurol Int. 2014;5:64. http://dx.doi.org/10.4103/2152-7806.132138
14. Sturm D, Bender S, Jones DT, Lichter P, Grill J, Becher O, et al. Pediatric and adult glioblastoma: Multiform (epi) genomic culprits emerge. Nat Rev Cancer. 2014;14(2):92–107. http://dx.doi.org/10.1038/nrc3655
15. Engelhard HH, Villano JL, Porter KR, Stewart AK, Barua M, Barker FG, et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equine. J Neurosurg Spine. 2010;13:67–77. http://dx.doi.org/10.3171/2010.3.SPINE09430
16. Adams H, Chaichana KL, Avendano J, Liu B, Raza SM, Quinones-Hinojosa A. Adult cerebellar glio-blastoma: Understanding survival and prognostic factors using a population-based database from 1973–2009. World Neurosurg. 2013;80(6):e181–3. http://dx.doi.org/10.1016/j.wneu.2013.02.010
17. Wang R, Chadalavada K, Wilshire J, Kowalik U, Hovinga KE, Fligelman B, et al. Glioblastoma stem-like cells give rise to tumor endothelium. Nature. 2010;468:829–3. http://dx.doi.org/10.1038/nature09624
18. Dirks PB. Brain tumor stem cells: Bringing order to the chaos of brain cancer. J Clin Oncol. 2008;26:2916–24. http://dx.doi.org/10.1200/JCO.2008.17.6792
19. Chen J, McKay RM, Parada LF. Malignant glioma: Lessons from genomics, mouse models, and stem cells. Cell. 2012;149:36–47. http://dx.doi.org/10.1016/j.cell.2012.03.009
20. Pollard SM, Yoshikawa K, Clarke ID, Danovi D, Stricker S, Russell R, et al. Glioma stem cell lines expanded in adherent culture have tumor-specific phenotypes and are suitable for chemical and genetic screens. Cell Stem Cell. 2009;4:568–80. http://dx.doi.org/10.1016/j.stem.2009.03.014
21. Wrensch W, Fisher JL, Schwartzbaum A, Bondy M, Berger M, Aldape KD. Molecular epidemiology of gliomas in adults. Neurosurgical Focus. 2005;19(5):1–11. http://dx.doi.org/10.3171/foc.2005.19.5.6
22. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of Glioblastoma multiforme. Nat Clin Pract Neurol. 2006;2:494–503. http://dx.doi.org/10.1038/ncpneuro0289
23. Hoschberg F, Toniolo P, Cole P, Scalcman M. Nonoccupational risk indicators of glioblastoma in adults. J Neuroincol. 1999;8:55–60.
24. Deltour I, Auvinen A, Feychting M, Johansen C, Klaeboe L, Sankila R, et al. Mobile phone use and incidence of glioma in the Nordic countries 1979–2008: Consistency check. Epidemiology. 2012;23(2):301–7. http://dx.doi.org/10.1097/EDE.0b013e3182448295
25. Benson VS, Pirie K, Schuz J, Reeves GK, Beral V, Green J. Mobil phone use and risk of brain neoplasms and other cancers: Prospective study. Int J Epidemiol. 2013;43(3):792–802. http://dx.doi.org/10.1093/ije/dyt072
26. Nieder C, Grosu A, Astner S, Molls M. Treatment of unresectable glioblastoma multiforme. Anticancer Res. 2005;1(25):4605–10.
27. Stummer W, Reulen H-J, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: Identification of and adjustment for bias. Neurosurgery. 2008;62(3):564–76. http://dx.doi.org/10.1227/01.neu.0000317304.31579.17
28. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96. http://dx.doi.org/10.1056/NEJMoa043330