Assessing the Risk Brain Tumors in Young Population: A Review

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***Abstract*—Brain tumors in the young population represent a significant and evolving public health concern becauseof their biological heterogeneity, rising incidence, and long-term impact on survival and quality of life. This review provides a comprehensive overview of the epidemiology, risk factors, tumor classification, diagnostic approaches, and therapeutic strategies for brain and central nervous system (CNS) tumors affecting children, adolescents, and young adults. Global epidemiological trends indicate a steady increase in CNS tumor incidence, with notable regional variations influenced by socioeconomic development and healthcare access. Genetic alterations, including distinct molecular and epigenetic signatures, play a pivotal role in tumor initiation and progression, whereas environmental exposures, particularly ionizing radiation and pollutants, remain important modifiable risk factors. Advances in neuroimaging, molecular diagnostics, and histopathological classification have improved early detection and tumor stratification in recent years. Current treatment modalities, including surgery, radiotherapy, and chemotherapy, remain central to management; however, therapeutic resistance and treatment-related morbidity continue to pose challenges. Emerging approaches, such as nanotechnology-based drug delivery systems, offer promising avenues for enhancing blood–brain barrier penetration and improving therapeutic efficacy. Despite these advances, limitations in data capture and variability in exposure assessment highlight the need for prospective studies and standardized methodologies. Overall, this review underscores the importance of integrated molecular research, early diagnosis, and innovative treatment strategies for improving outcomes in young patients with brain tumors.**

***Index Terms*—Brain tumors; Central nervous system neoplasms; Young population; Epidemiology; Risk factors; Molecular profiling; Neuroimaging; Treatment strategies; Nanotechnology; Prognosis**

I. INTRODUCTION

A brain tumor is characterized by abnormal and uncontrolled cell growth within the brain. In the context of malignant primary tumors like glioblastoma multiforme (GBM), it refers to a highly aggressive cancer that originates in the brain and is characterized by rapid cell proliferation, invasive growth into surrounding brain tissue, resistance to treatments, and a tendency to recur even after surgery, chemotherapy, and radiotherapy.[1] Central nervous system cancers represent a highly heterogeneous and histologically diverse group of neoplasms, most of which consist of malignant brain tumors.[2]

Recent WHO reports indicate a steady rise in brain tumor cases in India, driven by lifestyle changes, improved diagnostic facilities, an aging population, and overall population growth. Brain tumors are now among the top ten cancers in the country, highlighting the need for stronger treatment and support. Significant disparities in healthcare access, especially in rural regions, contribute to delayed diagnoses, limited specialist availability, and poorer outcomes.[3]

Glioblastoma is the most aggressive and commonly diagnosed primary malignant brain tumor in adults, accounting for approximately 45–50% of cases. Its global incidence is estimated at 3–5 per 100,000 individuals annually, with higher rates reported in developed countries. The disease predominantly affects older adults, peaking between 65 and 75 years of age, and shows a slight male predominance. Although observed across all populations, a higher incidence has been reported among individuals of Caucasian descent. The etiology of glioblastoma remains unclear; however, identified risk factors include genetic predisposition, exposure to ionizing

radiation, and inherited cancer-associated syndromes such as Li–Fraumeni syndrome and neurofibromatosis type 1. In contrast, lifestyle-related factors have not beenconsistently associated with this risk. The aggressive nature and poor prognosis of glioblastoma highlight the need for further research into its risk determinants and prevention.[4]

II. EPIDERMOLOGY OF BRAIN TUMORS IN YOUNG POPULATION

From 1990 to 2021, all 21 global regions showed an increase in the incidence of brain and central nervous system (CNS) cancers. In 2021, East Asia reported the highest absolute number of cases, totaling 16,032.6 (95% UI: 12,270.6–20,948.3). In contrast, Western Europe recorded the highest incidence rate at 4.3 per 100,000 population (95% UI: 3.9–4.6). Among all regions, the most rapid increase in incidence was observed in the high-income Asia-Pacific region, with an estimated annual percentage change (EAPC) of 2.79 (95% UI: 2.49–3.09).

Across socio-demographic index (SDI) categories, the middle-SDI group reported the highest disease burden, with 16,935.3 cases (95% UI: 13,670.1–20,391.3). Incidence rates generally increased with rising SDI levels, reaching a peak in high-SDI regions at 3.6 per 100,000 population (95% UI: 3.4–3.9). The most pronounced growth trend was noted in the low-middle SDI regions, which recorded an EAPC of 1.22 (95% UI: 1.18–1.27).

Over the past three decades, most regions have experienced an increase in both the absolute number of deaths and mortality rates associated with CNS cancers. In 2021, East Asia reported the highest number of deaths, reaching 6,064 (95% UI: 4,566.5–7,900.5). However, Central Asia exhibited the highest mortality rate at 2.4 per 100,000 population (95% UI: 2.0–2.9). The greatest increase in mortality rate was observed in Western Sub-Saharan Africa, with an EAPC of 1.56 (95% UI: 1.48–1.67).

Across SDI categories, the middle-SDI group again recorded the highest number of deaths, totaling 8,922.7 (95% UI: 7,208.7–10,649.8). Mortality rates tended to rise with increasing SDI, with high-middle SDI regions showing the highest mortality rate at 1.4 (95% UI: 1.2–1.7). The steepest increase in mortality was observed in low-middle SDI regions, with an EAPC of 0.86 (95% UI: 0.79–0.93).[5]

Projection of Brain and CNS Cancer ASR to 2040

Using an ARIMA forecasting model, future trends in the incidence, mortality, and DALY burden of brain and CNS cancers were estimated until 2040. The model suggests a gradual decline in incidence, with the age-standardized rate projected to fall from 4.28 per 100,000 in 2021 to 3.98 per 100,000 by 2040.

Similarly, the age-standardized mortality rate is expected to continue its downward trend, decreasing from 3.06 in 2021 to 2.70 per 100,000 by 2040.

A comparable reduction is predicted in the age-standardized DALY rate, which is forecasted to drop from 108 to 89 per 100,000 population over the same period.[6]

Risk factor for brain tumor in young population

Multiple mechanisms have been proposed to explain the pathogenesis of primary brain tumors, with substantial evidence implicating genetic alterations in their initiation and progression. Among environmental exposures, high-dose ionizing radiation remains the only well-established risk factor associated with the development of primary brain tumors.[7]

Gene factor

Gene expression profiling has been extensively applied to intrinsic brain tumors. Notably, ASPM overexpression has emerged as a potential molecular target in glioblastoma and medulloblastoma. In glioblastoma multiforme (GBM), significant alterations in the expression of genes involved in DNA repair and cell cycle regulation have been documented during tumor progression. Transcriptomic analyses have identified a 27-gene signature, along with distinct patterns of protein-coding genes (PCGs) and long noncoding RNAs (lncRNAs), offering additional insight into GBM biology and potential therapeutic avenues.

Gene expression profiling has revealed major molecular diversity in pediatric CNS tumors. Medulloblastoma comprises four distinct subgroups: WNT, SHH, Group 3, and Group 4, each driven by unique signaling pathways. WNT tumors show aberrant WNT/β-catenin and axon-guidance signaling; SHH tumors involve dysregulated developmental pathways and stem cell programs;and Groups 3 and 4 display activation of MAPK, glutamate receptor, phototransduction, p53, and semaphorin pathways. These differences underscore subgroup-specific

biology and the need for subgroup-specific therapeutic targets.

Similar transcriptomic analyses have refined the classification of ependymal tumors and uncovered biological heterogeneity in choroid plexus carcinoma. Diffuse midline glioma (DMG) is characterized by the global loss of H3K27me3, primarilydueto H3K27M mutations or EZHIP overexpression, both of which inhibit PRC2 function and lead to widespread gene activation. DMG cells also show metabolic reprogramming and vulnerability to SWI/SNF components, FOXO1, and phosphorylated STAT3. Upregulation of TGFB2 was associated with poor prognosis, whereas TGFB3 expression correlated with better outcomes. Spatial transcriptomics highlights distinct gene expression programs within tumor niches, including neuronal/OPC signatures in the tumor core and hypoxia-immune-reactive pathways in vascular and hypoxic regions. These molecular signatures offer valuable biomarkers and inform the development of targeted and radiotherapy-adapted treatment strategies.[8]

III. ENVIRONMENTAL FACTOR

Environmental pollutants are increasingly recognized as contributors to the biological processes underlying pediatric-brain-tumor development. Combustion-derived contaminants such as polycyclic aromatic hydrocarbons, particulate matter, nitrogen oxides, carbon monoxide, and sulfur dioxide can induce oxidative stress, DNA methylation changes, and aberrant gene activation, all of which are mechanistically linked to neurocarcinogenesis. Additional carcinogenic agents, including asbestos, benzene, gasoline exhaust, arsenic compounds, and persistent organic pollutants such as dioxins, further contribute to genotoxic and epigenetic alterations associated with brain tumor risk. Children are particularly susceptible to these exposures due to their ongoing neurodevelopment, and evidence suggests that residence in areas with high ambient pollution is associated with poorer survival outcomes in pediatric cancer. These findings underscore the need for focused genotoxicity, carcinogenicity, and epigenetic research to clarify the role of environmental pollutants in the etiology and progression of childhood brain tumors.[9]

Lifestyle factor

Participants showed adequate awareness of general lifestyle recommendations; however, their knowledge of specific exercise and dietary guidelines, especially fruit, vegetable, protein, and sodium requirements, was limited. Nearly half of the participants consumed processed foods recently, and fewer than one-fifth met the recommended fruit and vegetable intake. Dietary choices are frequently influenced by emotional factors such as stress, fatigue, and low mood.

Physical activity patterns varied, with moderate- and vigorous-intensity exercise reported on several days per week, and most individuals meeting at least 30 min of activity on active days. Time constraints, occupational and family responsibilities, low energy levels, and safety concerns were common barriers.

Sleep inadequacy was prevalent, with more than half of the participants reporting <7 hours of sleep and frequent nighttime screen use. Despite this, most participants reported adequate social support and a sense of purpose.

Stress levels ranged from mild to moderate, accompanied by intermittent feelings of being overwhelmed or low motivation. The coping strategies included exercise, meditation, counseling, and increased screen time.

Substance use was low overall, with minimal alcohol intake, low smoking prevalence, and negligible use of recreational drugs. Only a small proportion had received professional nutrition counseling.[10]

limitation

This study had several limitations inherent to its retrospective design. Key sociodemographic and behavioral data were incompletely captured due to the lack of routine telephone follow-up. Information on environmental and lifestyle exposures relied on patient recall and chart documentation, making variables such as secondhand smoke, sun exposure, and prior eye trauma susceptible to recall and recording biases.

Some data were obtained only through phone surveys when absent from medical charts, introducing potential missing data bias, likely affecting both cases and controls. Additionally, reliance on available records may have biased results toward surviving patients, as data for deceased individuals were often limited.

The study population was confined to patients treated with PBRT.Although no major differences in risk

factors compared with other ocular radiotherapy approaches have been reported, subtle variations cannot be excluded. These limitations underscore the need for prospective studies and more standardized exposure assessment during initial ocular oncology or radiation oncology evaluations.[11]

Types of brain tumor in young population

Brain tumors can be classified based on cell of origin, anatomical location, biological behavior, and histological grade. Broadly, they fall into four major categories: gliomas, meningiomas, pituitary tumors, and normal/non-neoplastic tissues for comparative purposes.[12]

In adults, the majority of gliomas arise from astrocytic lineages, accounting for approximately 75% of cases, with glioblastoma (GBM) representing the most aggressive form and comprising nearly two-thirds of malignant astrocytic tumors.[12]

The 2007 WHO classification grouped diffuse gliomas including astrocytomas, oligodendrogliomas, and mixed oligoastrocytic tumors into grades II (low-grade), III (anaplastic), and IV (glioblastoma) based on histopathological features. However, relying solely on microscopic evaluation poses limitations, as genetic alterations are often difficult to distinguish morphologically, and biopsy samples may not fully represent tumor heterogeneity.[3]

Diffuse gliomas exhibit diverse molecular signatures; oligodendroglial tumors, in particular, possess distinct genetic profiles that differentiate them from purely astrocytic gliomas.[3]

Gliomas

Gliomas are the most common primary tumors of the central nervous system and are typically managed using a multimodal approach involving maximal safe surgical resection followed by radiotherapy and chemotherapy.[13]

Their classification is guided by the WHO framework, which integrates histological and molecular features and assigns tumors to CNS WHO grades 1–4, reflecting increasing malignant potential. In adults, diffusely infiltrating gliomas encompass several tumor types, each characterized by distinct biological behavior and differential responses to therapy.[14]

Oligodendroglioma

Oligodendrogliomas and mixed gliomas are infiltrating tumors identified by the presence of oligodendroglial features, either alone or alongside astrocytic components, even when focal.[15]

Oligodendroglial tumors have gained prominence owing to their distinctive chemosensitivity and superior survival outcomes compared with astrocytic gliomas. These advantages are largely attributed to characteristic molecular alterations, particularly the 1p/19q co-deletion, which is a key diagnostic and prognostic biomarker. Conversely, aberrations such as CDKN2A deletion, PTEN mutation, and EGFR amplification predict poorer outcomes.[16]

Pituitary gland

Anterior pituitary neoplasms, historically referred to interchangeably as tumors and adenomas, have been recognized for over a century and are characterized by both hormonal hypersecretion and mass effects, even when small in size. Although most are benign and respond well to surgical and pharmacological management, a subset can demonstrate aggressive behavior, exhibiting rapid growth, radiologically confirmed invasion, or progression despite optimal therapy. Rarely, these tumors may metastasize, at which point they are classified as pituitary carcinomas. The former term “atypical adenoma,” defined by elevated mitotic activity, increased Ki-67 index, and strong p53 immunoreactivity, has been largely abandoned due to confusion with the clinically defined category of aggressive pituitary tumors.[17]

IV. SYMPTOMS AND DIAGNOSIS OF BRAIN TUMORS IN YOUNG POPULATION

Medical history and physical examination

The diagnostic process typically begins with a detailed medical history, including documentation of prior illnesses, presenting symptoms, and their durations. This is complemented by a comprehensive physical evaluation, followed by a focused neurological examination to assess cognitive status, reasoning ability, and motor coordination. Magnetic resonance imaging (MRI) is subsequently employed as it provides high-resolution visualization of intracranial structures and yields critical information regarding the location, dimensions, and morphological characteristics of suspected tumors.

Computed Tomography (CT) scans

Computed tomography (CT) is commonly used for the initial diagnosis of brain tumors due to its speed and

accessibility; however, radiation exposure, particularly in pediatric patients, necessitates cautious use and careful dose optimization.[18]

This study aimed to assess the feasibility of using a computed tomography (CT) scanner as a therapeutic platform for delivering radiation to human brain tumors (CTRx). This initial clinical application of a modified CT system for treatment was based on substantial preclinical evidence generated from prior investigations involving canine brain tumors.[19]

Blood tests

Peripheral blood was collected from eligible patients and healthy volunteers under IRB-approved protocols to evaluate circulating tumor cells (CTCs). Control samples established a baseline of 1.3 GFP-positive cells per milliliter for CTC detection. After discarding the first tube to avoid epithelial contamination, approximately 10 mL of heparinized blood was processed using OncoQuick centrifugation to enrich CTCs. The isolated cells were incubated with an adenoviral probe for 24 hours, fixed, and analyzed by semiautomated fluorescence microscopy using standardized criteria for fluorescence intensity, cell size, and exclusion of debris, enabling specific identification of tumor-derived cells.[20]

Functional Imaging

Ictal SPECT is most frequently employed in MRI-negative cases or when structural MRI findings are discordant with video-EEG data. In patients with low-grade tumors such as DNTs, ictal SPECT can reveal areas of hyperperfusion that extend beyond regions appearing normal on MRI, particularly when tumor-associated focal cortical dysplasia is present. These observations highlight that the epileptogenic zone may extend beyond the MR-visible lesion in certain DNT subtypes. Notably, the passage provides no specific information regarding the use of magnetoencephalography or positron emission tomography.[21]

V. TREATMENT AND PROGNOSIS OF BRAIN TUMORS IN YOUNG POPULATION

Surgery

Surgical intervention is considered the primary treatment modality for most pediatric brain tumor types, as chemotherapy and radiotherapy are associated with potential adverse effects on cognitive and neurodevelopmental outcomes in children.[22]

Precise preoperative functional mapping is essential to optimize the extent of tumor resection while preserving eloquent neural structures during brain tumor surgery.[23]

Over the past decade, the standardization of the surgical safety checklist has marked a significant advancement in operative care. However, complications continue to occur in approximately 25% of surgical patients. The World Health Organization–endorsed checklist incorporates universally applicable elements, including patient identification, operative site verification, blood product availability, and thromboembolism prophylaxis, and has been widely adopted as a benchmark for quality and safety becauseof its broad applicability. Although additional checklists have been implemented for various preoperative stages, the considerable diversity and procedure-specific requirements of modern surgical practices mean that important elements unique to individual surgeries may not be captured by the generic WHO checklist, and their omission may adversely influence operative outcomes and patient safety.[24]

Radiation

Radiation therapy, in combination with chemotherapy and surgery, plays a crucial role in achieving effective local disease control in pediatric malignancies.[25]

Radiation therapy (RT) is a fundamental component in the treatment of both primary and metastatic brain tumors, contributing substantially to improved intracranial disease control, overall survival, and symptomatic relief. Optimal radiation planning and delivery constitute critical components of the multidisciplinary approach to managing tumors such as gliomas, meningiomas, and brain metastases. Among primary malignant brain tumors, glioblastoma remains the most prevalent, and RT constitutes a central element of both initial therapy and subsequent salvage treatment strategies.[26]

Chemotherapy

Chemotherapy plays a crucial role in the management of malignant brain tumors; however, conventional systemic administration is frequently constrained by poor penetration of the blood–brain barrier and dose-limiting toxicities. Intra-arterial cerebral

chemotherapy has emerged as a targeted delivery strategy that allows higher regional drug exposure using agents such as carboplatin, methotrexate, and liposomal formulations. Clinical evidence from recurrent glioblastoma and primary central nervous system lymphoma suggests improved therapeutic outcomes, highlighting the need for further evaluation through randomized multicenter clinical trials.[27]

These agents were successfully co-encapsulated within mPEG-b-p(HPMAm-Bz) polymeric micelles, enabling effective dual drug delivery. Intravenous administration of the multidrug micelles demonstrated favorable tolerability and produced significant tumor growth inhibition in subcutaneous GL261 glioma models. Furthermore, in an orthotopic patient-derived DIPG model, the combination of multidrug micelles with ultrasound-mediated blood–brain barrier opening improved treatment response. These findings highlight the potential of synergistic chemotherapeutic combinations delivered through advanced nanocarrier systems to overcome current limitations in brain tumor therapy.[28]

Nanotechnology

Nanotechnology has revolutionized neuroscience by improving diagnostic and therapeutic approaches via enhanced BBB penetration and targeted drug delivery. Nanoneuroscience offers promising strategies for treating complex CNS disorders, including neurodegenerative diseases and brain malignancies.[29]

Nanotechnology has substantially redefined contemporary approaches to the assessment and treatment of neurological function, enabling significant advancements in both diagnostic and therapeutic modalities. This rapidly evolving interdisciplinary field, referred to as nanoneuroscience, exploits the physicochemical attributes of nanomaterials—most notably their ultrasmall dimensions, biocompatibility, tunable surface characteristics, and inherent capacity to traverse the blood–brain barrier (BBB). These properties facilitate the development of highly specialized platforms for managing central nervous system (CNS) disorders. By markedly enhancing drug-delivery efficiency and target specificity, nanotechnology offers considerable promise for addressing complex neuropathologies such as Alzheimer's disease, Parkinson's disease, and malignant brain tumors, wherein conventional therapeutic strategies are limited by inadequate BBB permeability and suboptimal localization to diseased neural tissues.[30]

VI. CONCLUSION

Brain tumors in the young population remain a major clinical challenge due to their biological diversity, rising incidence, and long-term treatment-related complications. Advances in molecular profiling and diagnostic imaging have improved tumor classification and management; however, therapeutic resistance and toxicity continue to limit outcomes. Emerging strategies, particularly nanotechnology-based drug delivery and targeted therapies, show promise in overcoming blood–brain barrier limitations and enhancing treatment efficacy. Future efforts should focus on integrated prospective research and early intervention strategies to improve the survival and quality of life of young patients with brain tumors.

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