Review

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Exploring neonatal brain tumors: a narrative review about epidemiology, classification, and management

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Abstract

Neonatal brain tumors (NBTs) are rare, with specific characteristics distinguishing them from tumors in older children. NBTs occur in the first 28 days of life with a low incidence rate. They present unique histological features, with teratomas and gliomas being the most relevant types of NBTs. The most common clinical finding is macrocephaly and hydrocephaly, but non-specific symptoms can also occur. Researchers illustrated multiple risk factors predominantly carcinogens and genetic factors. Managing these tumors is challenging, with surgery being the gold standard for treatment whereas the use of chemotherapy and radiotherapy is risky with this age group. Thus, balancing between aggressive intervention and adverse effects is crucial. This review will be relevant to clinicians and researchers interested in understanding the epidemiology, classification, clinical features, diagnostic features, and management options of NBTs.

Keywords: brain tumors, neonatal cancer, neonates, neuro-oncology

Introduction

Central nervous system (CNS) tumors can be either malignant or benign arising from neurogenic dysregulation and abnormal cellular growth[1]. They are the most prevalent solid cancer in children and responsible for the majority of cancer-related deaths, having an incidence rate of 5.14–6.23 cases per 100 000 people[2,3]. Globally, about 20% of pediatric cancer cases are brain tumors, and only 6.7% of these pediatric cases are infantile; physicians initially discovered them before the age of 1 year[4]. Although these infantile tumors have over 100 subtypes, their rarity makes research difficult[5].

Overall survival rates for infantile brain tumors are the lowest among similar disease groups[4]. Researchers ascribe these poor outcomes to limitations of radiation therapy in young individuals, biological variations, and chemotherapy difficulties[6]. Among infantile brain tumors, neonatal brain tumors (NBTs) are the rarest. They occur within the first 28 days of life and are distinguished from tumors later in childhood by specific histologic types, locations, behaviors, and prognoses contributing to diagnostic and therapeutic difficulties[7].

HIGHLIGHTS

- This article investigates the main aspects of neonatal brain tumors.
- It reviews the incidence, prevalence, and demographic factors of neonatal brain tumors, shedding light on any variations that might be present between populations.
- It discusses the various types of these tumors, emphasizing their clinical features.
- It summarizes the latest diagnostic and therapeutic approaches used.

The most relevant NBTs are teratomas and gliomas[7]. Researchers elucidated many risk factors primarily carcinogens, instrument-assisted birth, and genetic factors[5,8,9]. The gold standard treatment is surgery[10]. Age, tumor grade, type, and location are crucial in these tumors' development and treatment outcomes[11]. Thus, histopathological and neuropathological assessments improve patient risk classification, correct diagnosis, and treatment strategies[10]. In this review, we aim to summarize the current knowledge on the epidemiology, classification, clinical features, diagnostic features, and management options of NBTs.

Definitions

Pediatric brain tumors are categorized based on the timing of diagnosis and the age of the patient. Infantile brain tumors represent a broad group encompassing all brain tumors diagnosed during the first 12 months of life, with some studies expanding this period to 2 years[3]. Common symptoms include vomiting, macrocephaly, headache, and psychomotor

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changes[3]. These tumors are usually diagnosed after the development of symptoms[11]. NBTs, diagnosed within the first 28 days of life, are a rare subset of infantile brain tumors specifically identified within the neonatal period[12]. They are classified according to the clinical presentation into: prenatal, perinatal, and postnatal[13]. NBTs have a poor prognosis and typically manifest with symptoms of increased head circumference, irritability, and neurologic complications shortly after birth[7].

"Congenital brain tumors" is not a universally accepted term and lacks a clear definition. Some studies classified this subgroup into "definitely congenital" when symptomatic at birth, "probably congenital" when symptomatic within the first week of life, and "possibly congenital" if symptomatic within the first 6 months of life[11,13]. Other studies define this term as those detected prenatally or within the first 2 months of life[11]. Advances in prenatal and neonatal screening now enable the detection of the "probably congenital" group[13].

Epidemiology

NBTs have an incidence rate of 0.5–1% in neonates[7]. However, some variations may occur due to differences in diagnostic procedures between countries and a lack of pediatric data in some regions[9]. An interaction between genetic, environmental, and demographic factors modulates their prevalence[8]. Researchers have recognized multiple risk factors, such as ionizing radiation exposure, genetic abnormalities, birth defects, prenatal growth indicators, advanced parental age, and maternal consumption of N-nitroso compounds[14]. Notably, high-grade gliomas (HGGs) are more common in neonates under three months than low-grade ones (LGGs)[15]. Embryonal tumors frequently occur in newborn and infant populations, with a decrease in incidence as children grow, highlighting the importance of age-specific considerations in tumor subtypes and therapeutic options[15].

Newborn survival rates are often lower than those reported in older age groups since neonates frequently get less aggressive therapies[5,15]. The incidence of different subtypes was heterogeneous within different series and related to racial and regional factors[11,16-18] (Fig. 1). Sexual disparities are noted, in which males are more likely to develop choroid plexus, embryonal, and ependymal tumors than females[19]. Understanding these multiple epidemiological determinants is crucial for improving prevention, diagnosis, and treatment modalities for newborns[14,20].

Using fetal magnetic resonance imaging (MRI) and prenatal anomaly scans, physicians have recently detected brain tumors and evaluated their severity during fetal development. Depending on gestational age, fetal MRI can increase diagnostic accuracy by up to 29%[21]. Furthermore, by improving image segmentation and decreasing diagnostic mistakes, the use of machine learning approaches in the analysis of newborn MRI images has increased detection rates[22].

As molecular diagnostics play a role in tumor classification, guided by the World Health Organization (WHO) classifications from 2016 and 2021, new tumor types are being introduced while others are being eliminated, altering the reported frequencies of tumor types in the future[21].

Classification

The classification and distribution of NBT subtypes differ from those seen in older children[7] (Fig. 2). Teratoma is the most

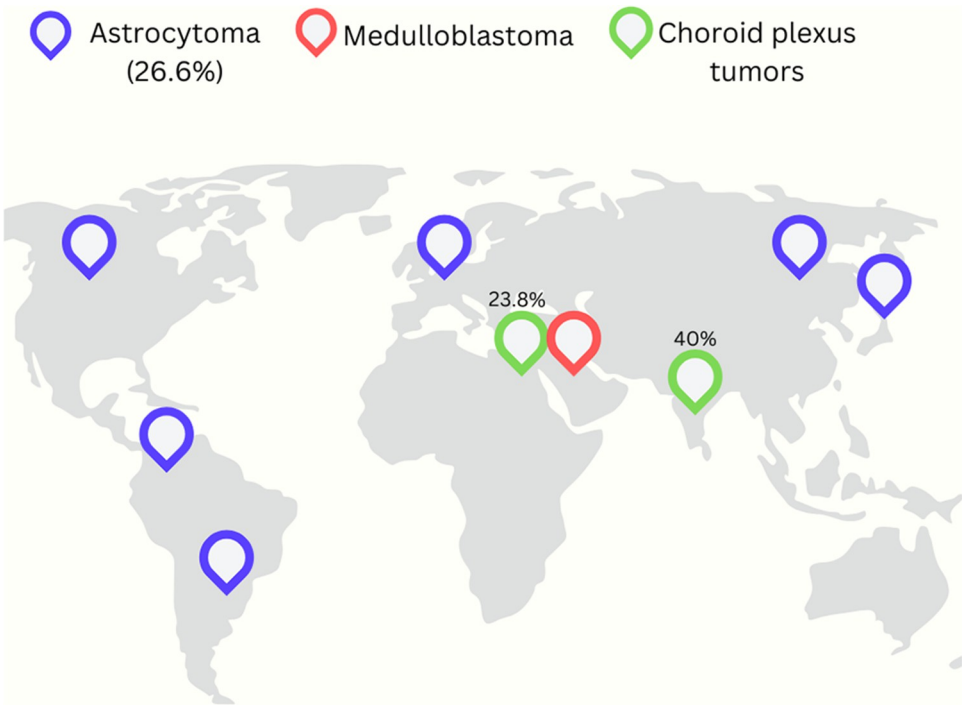

Figure 1. The most common pediatric brain tumor in Europe, United States of America (USA), Canada, Mexico, Argentina, Japan, and the Far East is astrocytoma (26.6%). Choroid plexus tumors are frequent in Egypt (23.8%) and India (40%), and medulloblastoma in Saudi Arabia.

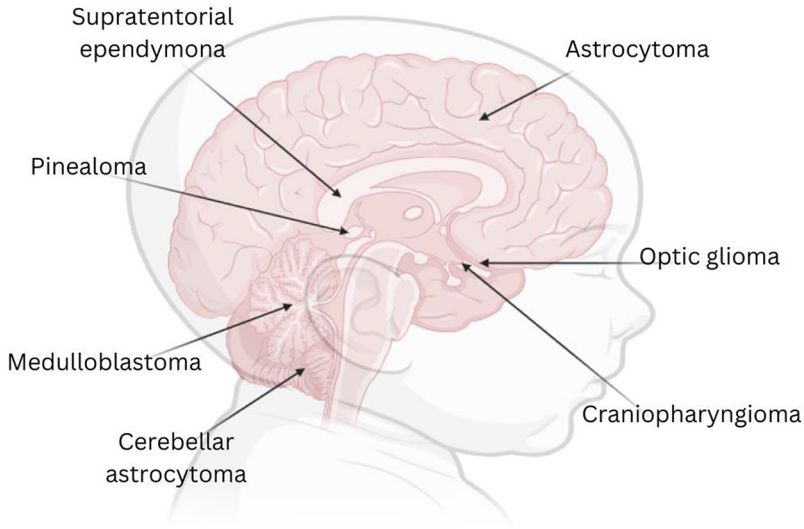

Figure 2. Common locations of brain tumors in neonates.

frequent congenital tumor followed by gliomas and choroid plexus papillomas (CPPs)[3]. Other subtypes are embryonal tumors constituting medulloblastoma (MB), atypical teratoid/rhabdoid tumors (AT/RTs), and embryonal tumors with multilayered rosettes[23]. Additionally, other rare forms such as pineoblastoma, craniopharyngiomas, and hypothalamic hamartoma (HH) may occur[7,24]. Regarding locations, uniquely 74.3% of tumors were found in the supratentorial region, while infratentorial tumors accounted for 25.7%[2].

Germ cell tumors

This subtype includes teratoma, which accounts for 25–55% of cases[7]. Most often, all germ layers (ectoderm, endoderm, and mesoderm) give rise to teratomas, which may appear as mature or immature[3]. They are usually found in supratentorial or suprasellar regions, or the pineal gland. Imaging reveals a large, heterogeneous mass of solid and cystic components, calcification, fatty deposits, and sometimes bone or teeth[9]. Surgical resection is the main treatment for teratomas, while chemotherapy may benefit immature teratomas[7].

Table 1

Differences between HGGs and LGGs

Tumor type	Histological patterns (25)	Imaging biomarkers (26)
HGG	• Significant cellular atypia • Necrosis • High mitotic activity	• High sRCBV/ADC ratio • High rCBV (with median values of 2.54 mL/100 mL)
LGG	• Well-differentiated cells • Few mitotic figures • Low proliferation rate	• Low sRCBV/ADC ratio • Low rCBV (with median values of 1.68 mL/100 mL)

Glial tumors

These tumors are categorized based on their histological pattern and imaging biomarkers into LGGs and HGGs[25,26] (Table 1). Most LGGs (WHO classification grades I and II) are astrocytomas. They are more common in older children than newborns and include pilocytic, pilomyxoid, diffuse, and pleomorphic astrocytoma[7]. These tumors commonly originate in the supratentorial region (mesencephalon, pons, optic nerve, and hypothalamic/chiasmatic region)[6]. Pilocytic astrocytomas frequently occur in the cerebellum[23]. However, HGGs (WHO classification III and IV) are rare and specially arise from gene fusions. They can be either astrocytoma or glioblastoma multiforme (GBM)[11]. Midline tumors present more often in HGGs[2]. Despite enhanced surgical and other therapeutic methods, HGG patients are still at a higher risk for long-term complications[7].

Choroid plexus tumors

This subtype develops from the epithelial lining of ventricles, predominantly the lateral ventricle[13]. Bilateral ventricular occurrence is uncommon[13]. According to WHO classification, this group includes CPP (grade 1), atypical CPP (grade 2), and choroid plexus carcinoma (CPC) (grade 3)[13]. CPCs present poor prognoses due to tumor protein P53 gene (TP53) mutations[7]. On imaging, they appear as intraventricular masses with homogenous contrast enhancement[9]. Although papillomas are usually associated with a good prognosis and surgical outcome, generally, there's a risk of bleeding due to neonatal fragile vascularity[7,13].

Embryonal tumors

Embryonal tumors develop from neuroepithelial cells that are either undifferentiated or poorly differentiated[7]. MBs in infratentorial regions are more commonly present in older children than neonates. Imaging shows solid, homogenous masses, with or without cystic changes or calcification. The WHO classification

distinguishes four molecular groups. The Wingless-type (WNT)-activated group usually presents with low risk[7,27]. Sonic Hedgehog (SHH)-activated-and TP53-wildtype group is divided into two subgroups SHH β and SHH γ, which are associated with different outcomes. SHHβ are more aggressive, with a higher metastatic rate associated with primitive neuroectodermal phosphate and tensin homolog deletions, and are a high-risk group. While SHH γ have MB with extensive nodularity mutation, making it a low-risk group that doesn't require chemotherapy[3,27]. The SHH-activated and TP53-mutant group is rare. The fourth group is non-WNT/non-SHH and may benefit from gross resection[27]. SHH-driven cases are associated with a higher risk of developing Gorlin Syndrome (PTCH1-gene mutation) and skin cancers[7].

AT/RTs originate mainly in the posterior fossa but can manifest in any other region of the CNS with a potential for dissemination[28]. Most of these tumors arise due to SMARCB1 defect and are subdivided into three molecular groups (AT/RT-SHH, AT/RTTYR, and AT/RT-MYC)[27]. The WHO has also recognized pituitary blastoma, a rare embryonal tumor found in infants, as a distinct type of pituitary tumor[29]. It is a feature of DICER1 syndrome, an inherited disorder linked to a high risk of developing various hereditary tumors, including those of the kidney, thyroid, and brain. There is unclear data on whether pituitary blastomas are low- or high-grade tumors, but it's estimated that about 50% of affected children die[29]. WHO CNS5 brought significant diagnostic advances. This classification emphasized the importance of including molecular characteristics alongside histological features when categorizing CNS tumor types[29,30]. Additionally, updates from the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy further refined these classifications[31,32].

Hypothalamic hamartomas

HHs are generally small benign malformations of gray matter. These slowly growing structures consist of hyperplastic neurons located at the base of the brain, specifically in the third ventricular floor, close to the tuber cinereum and mammillary bodies[24].

Clinical features and symptoms

The clinical signs of CNS tumors in newborns can differ. Based on when symptoms arise, many experts categorize tumors as definitively congenital if signs are present during the prenatal phase or at the time of birth, probably congenital if symptoms manifest within the initial week of life, and possibly congenital if they occur within the first 6 months after birth[9]. Some symptoms associated with specific subtypes in infancy, such as HH and gelastic epilepsy, are well-known[7]. HGGs have a sudden onset with swift symptom progression, while LGGs usually develop over extended periods[23]. Macrocephaly and hydrocephalus may be noted as indirect signs of NBTs[7,9].

The onset of postnatal issues occurs slowly, characterized by persistent macrocephaly or rapid increases in head circumference, and may be accompanied by bulging fontanelles or delayed suture fusion[7]. Increased head circumference is a common presentation due to the expansile nature of the skull allowing extensive tumor growth, and this accounts for the subtle nature of symptoms. Other nonspecific symptoms may include drowsiness, irritability, vomiting, apnea, developmental delays, stunted growth, or unusual eye movements. Complications such as intramural tumoral bleeding or seizures can present suddenly[9]. An increase in amniotic fluid (polyhydramnios) is often the initial indication of a tumor with prenatal onset and is observed in the second to third trimesters of pregnancy due to hypothalamic dysfunction and increased cardiac output[21].

Macrocephaly is the main presentation and can occur due to intracranial tumoral growth, hydrocephalus from blocked ventricles, excessive cerebrospinal fluid (CSF) production, or bleeding in the brain from the cancer itself. Thus, normal brain development may be disrupted[3,9]. Some studies suggest that this sign may be asymptomatic due to the flexibility of a newborn's skull. Thus, neurologic immaturity in neonates often prevents the manifestation of specific symptoms observed in older children[3]. Elevated cranial pressure may cause bulging fontanelles, irritability, lethargy, apneic episodes, and seizures[33]. Uncommonly, large vascular tumors can lead to high-output heart failure[9].

In some reported cases of teratomas, primitive neuroectodermal tumors, and glioblastomas, the mass rapidly grows, leading to an enlarged skull, obstructed labor, or fetal death[2].

Concerns for pilomyxoid astrocytoma should be raised by the presence of intralesional hemorrhage, necessitating an evaluation for CSF seeding[29]. AT/RTs can present with a broad range of symptoms in the suprasellar region such as headache, double vision, subarachnoid hemorrhage, diabetes insipidus, and panhypopituitarism[34].

The clinical presentation of gliomas varies based on the tumor's location. Brainstem gliomas may present with hydrocephalus, fatigue, headaches, visual disturbances, ataxia, facial weakness, and gagging, whereas cortical gliomas often result in focal neurological disability[23]. Pilocytic astrocytomas can cause mass effects, which manifest depending on the tumor's size and location, leading to hydrocephalus and signs of increased intracranial pressure[7,23].

Diagnosis

Many brain tumors in children go undetected until they grow significantly because infants have expandable skulls and their developing brains can often compensate for neurological deficits[10]. Understanding the classification of brain tumors and their relevant imaging characteristics is essential, as the imaging phenotype can be a proxy for molecular diagnosis[30]. Prenatal US can detect an intracranial mass, which might be solid, cystic, or calcified. While calcifications are more clearly seen in computed tomography (CT), this imaging method is not employed in neonatal environments because of the radiation exposure risks[9]. Prenatal US evaluates the lesion's location and surrounding anatomical structures[35]. However, a histological investigation must be performed following delivery and indirect signs such as macrocephaly and hydrocephalus may be detected[3,9]. MRI poses a lower risk to the growing brain than CT, producing high-quality images of tumor morphology and anatomical relations[29].

CT and MRI are useful for finding cancers but have difficulties discriminating between different tumor kinds and grades[36]. One study revealed that among the radiological features of MRI scans for pediatric brain tumors, only the growth pattern and the presence of a cystic component correlate with the tumor's grade of malignancy[25]. Specifically, an infiltrative growth pattern is

associated with HGG, whereas the presence of a cystic component is linked to low-grade tumors[25]. Advanced MRI techniques such as diffusion-weighted imaging, diffusion tensor imaging, functional MRI, arterial spin labeling perfusion imaging, MR spectroscopy, and MR elastography improve our understanding of a tumor's structure and function[37]. For instance, in MR spectroscopy elevated levels of creatine and lactate metabolites in children with diffuse fibrillary WHO grade II astrocytoma help differentiate it from WHO grade I pilocytic astrocytoma. For supratentorial tumors, a significantly high myoinositol level is characteristic of CPP, differentiating it from other neoplasms and CPC[36]. MR spectroscopy distinguishes post-therapy changes from tumor recurrence, and neoplastic from non-neoplastic processes. Pediatric brain tumors often display a consistent metabolite profile during relapse, making MR spectroscopy useful for comparing patterns with the original tumor and enhancing diagnostic certainty regarding radiological recurrence[36].

With positron emission tomography and single-photon emission CT, radiotracer probes provide excellent insights into tumor metabolism and physiology[36]. Researchers could recognize most LGGs with high tracer uptake, even when MRI showed no enhancement for these tumors[36]. Furthermore, radiomics and radiogenomics are developing techniques for predicting tumor subtypes, molecular classification, and prognostication[38]. A CSF liquid biopsy is an approach for fast and noninvasive diagnosis and follow-up of CNS tumors. It adapts treatment to the patient's genetic alterations[39]. Cornelli, *et al* have highlighted the possibility of diagnosing and categorizing pediatric brain tumors based on methylation profiling of the circulating cell-free DNA in CSF[40].

Management

Despite all the improvements in molecular biology and surgical techniques, managing brain tumors in infants under 1 year of age is challenging. Many aspects should be considered because the newborn is not simply a small adult; even the biological characteristics of NBTs differ from those of other pediatric brain cancers[4]. Balancing treatment approaches and consequences can enhance long-term survival without lowering patients' quality of life[4,41]. Managing all treatment-related issues for these patients requires a dedicated multidisciplinary team consisting of a neonatologist, pediatrician, pediatric neurologist, pediatric oncologist, radiation oncologist, pediatric neurosurgeon, pediatric anesthesiologist, neuro-psychologist, physiotherapist, and nursing staff[42]. A multidisciplinary interview with parents is crucial to provide comprehensive counseling including treatment options, prognosis, and potential risks for the neonate or mother and fetus if the diagnosis was in the prenatal period[9]. Differentiating between histological types, such as distinct embryonal tumors, LGGs, and HGGs can direct suitable treatments for affected children and may ultimately influence their prognosis. Treatment approaches mainly include surgery, chemotherapy, radiation, and drug therapy[7,34,43].

Surgery

Surgery is the first option for most NBT types because chemotherapy and radiotherapy hold mental growth risks in children[10]. Intraoperative imaging techniques, such as intraoperative MRI and real-time ultrasound, can help localize tumors and confirm the extent of surgical resection. Also, intraoperative neurophysiological monitoring (IONM) can identify and control cranial nerves and brain regions, maintaining brain function[42]. IONM can help preserve brain function and is indispensable in resecting deep brain tumors, e.g., in the posterior fossa, and spinal cord tumors. Distinctions can be made among glial, ependymal, and embryonal tumors, intraoperative evaluation offers valuable insights that guide the surgical approach and establish a preliminary diagnosis. These techniques have become increasingly significant for patient care in recent years[44,45].

Research suggests that although surgical intervention is essential for treating pediatric AT/RTs, the impact of how much tissue is removed during surgery remains uncertain[34]. Hemorrhage during surgery is a major cause of raised mortality in low-body-weight neonates; therefore, one of the most important difficulties lies in evaluating the risks of doing early surgery on low-body-weight newborns vs. stalling the surgery until body weight increases with potential tumor progression[4]. A cohort study for infants with congenital brain tumors suggested postponing surgery until the patient is 1.3 months old and weighs more than 5.2 kg with short-term imaging follow-up, except if the tumor grows and causes significant neurological damage[4]. After surgery, a qualified staff should provide immediate intensive care for the neonate patient[42].

Chemotherapy

Chemotherapy may act as a short-term solution until radiation therapy can be safely started later on. It is the only acceptable adjuvant treatment at young ages[42,43]. Prenatal treatment primarily manages secondary complications arising from these tumors[46]. However, chemotherapy is not without challenges; neonates treated with chemotherapy often suffer from delayed growth, requiring close endocrinal monitoring, and long-term neurocognitive decline, which can result in unfavorable adult outcomes like decreased education levels and unemployment, ototoxicity, nephrotoxicity, and second cancers[47,48].

Radiation therapy

As for adjuvant therapies, irradiation is avoided under three years of age due to serious consequences, such as long-term cognitive and growth problems, endocrine malfunctions, and the possible development of secondary tumors in the CNS[9]. In infants with extremely radiosensitive tumors, high-dose chemotherapy is administered until the child is three to 5 years old, at a point when radiation therapy is less harmful to the brain[9,42]. However, early radiotherapy may be essential sometimes, and postponing it can lead to worse outcomes. For example, neonates with localized ependymoma should receive instant postoperative conformal radiotherapy for children as young as 12 months. Researchers suggest directing the patient to a pediatric proton center since proton beam irradiation reduces the side effects of radiotherapy, in addition to using lower dosages for extremely young pediatrics[49].

Targeted drug therapy

Over the last four decades, scientists have made numerous efforts to discover more effective drug therapies, but the results

were limited[50]. A significant factor contributing to this challenge is the blood–brain barrier (BBB), which hinders the passage of many medications into the brain[50]. Unsuccessful delivery of drugs is one of the agents leading to the failure of new treatments in the early stages of clinical trials after exhibiting remarkable preclinical efficacy. Research efforts over the last 10 years showed that not all childhood brain tumors affect the blood–brain tumor barrier (BBTB) in the same way. Instead, BBTB function is diverse among tumor types and even within individual tumors[51]. Lomustine, temozolomide, carmustine wafers, and everolimus are the four medications that the Food and Drug Administration (FDA) and European Medicines Agency approved for treating brain tumors. In contrast, other drugs used in pediatric brain tumors are experimental or off-label[52]. Although alternative methods of CNS drug administration are available to ensure that drugs achieve effective concentrations in tissues, three of these medications were chosen because of their ability to cross or bypass the BBB[50].

Advancements in NBT immunotherapy are promising. Transcriptomic analyses have revealed potential targets, such as antigen processing machinery and inhibitory checkpoint receptors, which could enhance treatment effectiveness[53]. Therapies like chimeric antigen receptor T-cell therapy, oncolytic virotherapy, and tumor vaccines are being explored and have shown promise in early trials[54]. Additionally, combining immunotherapy with other treatments, such as epigenetic drugs, may improve efficacy by addressing multiple pathways involved in tumor progression and immune evasion[55]. For example, a study found that combining adenoviral vector expressing Flt3L (Ad-Flt3L) and adenoviral vector expressing thymidine kinase for glioma therapy showed increased levels of dendritic cells and T-lymphocytes within the tumor microenvironment[56]. The first human phase 1 trial combined Ad-Flt3L and herpes simplex virus type 1 thymidine kinase gene therapy for resectable gliomas and induced the recognition of tumor cells by the brain's immune system[56]. However, most studies on immunotherapy in neonates are still in early phases, limiting insights into long-term benefits and survival rates[54].

Prognosis

The prognosis is typically unfavorable, with postnatal survival rates ranging from 16% to 28%, and in other studies, it ranges below 30%[9,21]. The outcomes are influenced by the type of tumor histology, its growth patterns, and the age of diagnosis[21]. Each tumor type presents distinct therapeutic targets, necessitating a careful treatment approach. Understanding the molecular mechanisms driving these tumors has facilitated the creation of targeted therapies[50]. Genetic profiling techniques, such as methylation analysis and exome sequencing, can pinpoint specific tumor subtypes and mutations[28]. Additionally, specific genetic alterations such as isocitrate dehydrogenase in gliomas is considered as a positive prognostic biomarker while cyclin-dependent kinase inhibitor 2A deletions and telomerase reverse transcriptase promoter indicate higher malignancy and worse outcomes[57]. Counseling should involve a multidisciplinary approach, addressing both the prognosis for the fetus and potential complications for the mother[21].

Future directions

A deeper molecular comprehension of these tumors may reveal new targeting agents and potentially lead to novel treatment strategies based on biology[3]. Scientists expect that activating the role of targeted therapy will improve the prognosis[42]. Anaplastic lymphoma kinase (ALK), a significant oncogenic driver in multiple cancers, has been studied recently in pediatric brain tumors. ALK fusions are recurrent genomic modifications, particularly in congenital glioblastoma, and manifest in infants in the same age category as those tumors now classified as "infant HGGs" by the WHO in 2021[58]. Seven case reports have been published about patients with ALK-rearranged infant-type hemispheric glioma who received lorlatinib (a third-generation ALK inhibitor); out of seven patients, four showed partial responses and one achieved a complete response, with event-free survival lasting for 6 to 22 months in six patients[59]. The significant regressions observed in ALK-rearranged gliomas exposed to various ALK inhibitors present advantages in various ALK fusions[58]. However, further studies are needed to refine the treatment timing[58].

Johnston, *et al* recently reconstructed the three-dimensional (3D) genome of Posterior fossa group A (PFA) ependymoma and have identified a notable characteristic unique to PFAs: type B ultra-long-range interactions in PFAs (TULIPs), which are regions located distantly along the linear genome that exhibit unexpectedly strong interactions in the 3D nuclear space[60]. Although TULIPs may be showing promising results, translating this knowledge into effective treatment is challenging[61].

Lactylation targeting is another strategy. Lactate-mediated protein lactylation is a post-translation modification that happens on both core histones and non-histone proteins, affecting gene regulation and cellular processes[62]. According to the Warburg effect, many tumor cells use aerobic glycolysis to produce energy, fermenting glucose to lactate even when oxygen is present. This phenomenon leads to lactate accumulation in the cancerous cells, making lactylation targeting a promising therapy in brain malignancies[62].

As for the challenge of drugs reaching the CNS, carbon dots (CDs) may be an innovative therapeutic method as a drug delivery system, in addition to their role in tumor imaging. CDs can penetrate the BBB efficiently, and the kidneys can excrete them without accumulating in the liver or spleen[63]. Furthermore, CDs can be highly modified for many drugs and tumor receptors and functionalized to encounter tumor heterogeneity and drug resistance while minimizing the effects of drugs on non-tumor cells[64]. These distinctive features make CDs a promising option for pediatric brain tumor therapy and represent hope for developing individualized treatments[65]. However, achieving high efficacy and selectivity in targeting tumor-specific ligands is still challenging[65].

In a short time, tumor-treating fields (TTFields) may be a safe local therapeutic approach instead of radiotherapy. TTFields therapy is a non-invasive locoregional therapeutic technique that uses alternating electric fields to apply antimitotic impacts on malignant cells. A portable device creates the fields, which are transmitted to the tumor using arrays applied to the scalp[66]. FDA in the United States and its international counterparts have approved TTFields therapy for the treatment of GBMs in adults[67]. According to the findings of Goldman, *et al*, children

with HGGs and other brain cancers had a good safety report for TTFields therapy, with primarily slight to moderate localized skin adverse events and no unforeseen toxicities[66].

Recently, applying artificial intelligence in medicine has opened a wide scope[68]. In medical image analysis, brain tumor segmentation is a critical procedure that attempts to identify the regions impacted by a tumor[69]. Major automated segmentation systems have been developed for adult brain tumors; therefore, they don't adapt well to pediatric ones. Until now, 3D Convolutional Neural Networks for pediatrics have not been utilized to their optimal level, thus physicians evaluate responses in these patients through two-dimensional measures[68,70]. Fathi Kazerooni, *et al* have shown an automated deep-learning model for pediatric tumors, providing standard measures in clinical and research applications[70].

Conclusion

In conclusion, NBTs are rare and constitute a heterogeneous group of tumors with distinct epidemiological and clinical behaviors. They have unique features regarding their symptoms, survival rate, and management. They have a poor prognosis, mainly due to the inability of this age group to tolerate the toxicity of radiotherapy and chemotherapy. Thus, treatment options are limited to surgery. Extensive research has examined the molecular makeup of pediatric brain tumors, leading to the new WHO classification's greater focus on molecular characteristics over histological structure alone. Although pediatric brain tumors have been better understood and managed, there is still a lack of studies focusing on the neonatal group. Effective management of NBTs requires a multidisciplinary approach and an in-depth understanding of neonatal biological characteristics. Further research on diagnosis and targeted treatments is needed to address the challenges posed by NBTs and improve survival rates in this population.

Ethical approval

This study did not involve human participants or animals, so no ethical approval or consent to participate was required.

Consent

All authors have reviewed the manuscript and consent to its publication.

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