Neonatal Central Nervous System Tumors

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KEYWORDS

• Neonatal brain tumor • Neonatal CNS tumor • Congenital brain tumor
• Congenital CNS tumor • Fetal brain tumor • Fetal CNS tumor

KEY POINTS

- Neonatal brain tumors represent less than 2% of all childhood central nervous system (CNS) tumors; however, they are associated with significant morbidity and mortality.
- The most common neonatal CNS tumor is teratoma; however, other histologies, such as astrocytoma and glioma, ependymoma, atypical teratoid/rhabdoid tumors, medulloblastoma, choroid plexus tumors, and craniopharyngiomas, also can be seen.
- Management options for neonatal CNS tumors often are limited due to the ability of newborns to tolerate surgery, radiation, and/or chemotherapy.
- A multidisciplinary approach is critical to address the psychosocial and medical challenges of these cases.

INTRODUCTION

Central nervous system (CNS) tumors are the most common solid tumors among children, but they are relatively rare in newborns. Although cooperative group studies generally have considered tumors occurring in children under the age of 3 years infant tumors, neonatal brain tumors are a unique entity that deserve more scrutiny. Multiple prior studies have more specifically established neonatal brain tumors as tumors diagnosed prenatally or in the first 2 months of life.[1,2] For the purpose of this review, the terms, *neonatal*, *perinatal*, and *congenital*, are used to refer to this same entity. Most reports suggest only approximately 0.5% to 1.9% of brain tumor cases occur during the perinatal period,[3,4] with an incidence ranging from 0.3 to 2.9 cases per 100,000 live births.[5] Biologically, congenital brain tumors are distinct from those occurring in older children. Supratentorial tumors are much more common than

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infratentorial tumors in neonates, and the prognosis and survival outcomes in this age group are much worse compared with those in older children.[6] Management is difficult with limited options for surgery and radiotherapy, given the concern for mortality and acute and late morbidities. The true rate of perinatal brain tumors may be underestimated because many may go undiagnosed due to intrauterine fetal demise. Although gliomas are the most common type of brain tumor in children of all ages, including infants (less than 3 years old [**Fig. 1**][7]), teratomas are the most common brain tumors in neonates, with astrocytoma, choroid plexus papilloma (CPP), embryonal tumors, and craniopharyngioma seen less frequently.

PRENATAL DIAGNOSIS AND IMAGING

With advanced fetal ultrasonography (US), many neonatal brain tumors are diagnosed prenatally, although histologic confirmation still typically has to be done after birth. Routine US examinations may miss fetal brain tumors as the brain undergoes rapid growth and development near the end of the third trimester. Teratomas and hamartomas may be detected before 22 weeks, germinal tumors between 22 weeks and 32 weeks, and gliomas after 32 weeks.[4] Prenatally, tumors can cause hydrocephalus, although the fetal skull can expand to a remarkable extent leading to macrocrania, or local skull swelling. For large tumors, this may lead to fetal hydrops requiring cranial decompression to permit vaginal delivery. Cesarean section is necessary in approximately two-thirds of these cases.[3]

Hydrocephalus, secondary to tumor growth or intracranial hemorrhage and obstruction of the ventricular system, often leads to symptoms of irritability and vomiting after birth. The fetus also may experience high-output heart failure, which can lead to stillbirth. Newborns also can present with seizures and somnolence. Occasionally, congenital brain tumors can be accompanied by other malformations, such as cleft lip/palate and cardiac and urinary tract defects. A recent population-based cohort study of 5.2 million children in Norway and Sweden revealed an increased risk of brain/CNS malignancy, specifically in children with oral clefts in the cohort from Sweden. In both countries, the risk for CNS cancer in the first year of life was increased in children with multiple birth defects. Birth defects also were found to have an increased association with medulloblastoma (MB), primitive neuroectodermal tumor, and germ cell tumors in a separate retrospective study of 3733 patients with brain tumors in the California Cancer Registry.[8]

US is the imaging modality used most commonly in the prenatal period; however, once a diagnosis of a brain tumor is suspected, fetal magnetic romance imaging (MRI) may help determine the exact location of the tumor, involvement of adjacent structures, and the developmental state of the remainder of the brain, which can help with prognosis and preparation for potential surgical intervention.[3] US may demonstrate a heterogeneous pattern with destruction of normal structures and mass effect and document the presence of hydrocephalus or calcifications in the case of teratomas. Importantly, prenatal diagnosis can help determine timing and route of delivery, prepare health care teams for postnatal management, and allow time for prenatal parental counseling regarding prognosis and therapeutic options.

TYPES OF NEONATAL BRAIN TUMORS

Germ Cell Tumors

Histologically, intracranial germ cell tumors are composed of germinomas and nongerminomatous germ cell tumors (NGGCTs). The NGGCT category comprises of multiple histologies, including teratomas, teratomas with malignant transformation, yolk

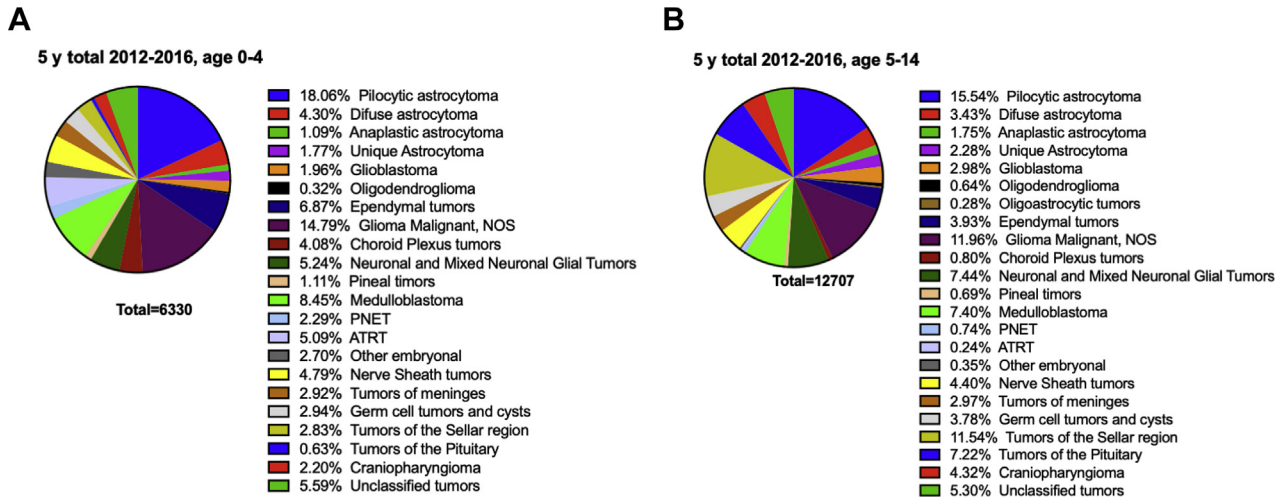

Fig. 1. Distribution of brain tumor diagnoses among children between the ages of (*A*) 0 to 4 years and (*B*) 5 years to 14 years based on the incidence of CNS tumor diagnosed in the US population from 2012 to 2016 and presented in the Central Brain Tumor Registry of the United States (CBTRUS) statistical report.[7] Note the higher incidence of embryonal tumors (AT/RT, ETMR, pineal tumors, MB, and other embryonal) and choroid plexus tumors among the younger age group.

sac tumors, choriocarcinoma, embryonal carcinoma, and mixed germ cell tumors.[9] Teratomas are the most common brain tumors in the neonatal period, constituting 33% to 50% of all cases.[10,11] They are derived from all 3 germ layers (ectoderm, mesoderm, and endoderm) and can present as mature or immature forms. Neonatal teratomas can be located anywhere along the midline, with the sacrococcygeal region being most common.[10] In the brain, they often are located in the pineal region or the neurohypophysis or adjacent to the third ventricle.[4,12] These also can involve the hemispheres in neonates. Sometimes teratomas may be associated with elevation of alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (beta-HCG) in the serum and cerebrospinal fluid (CSF).[13] Symptoms vary based on location and extent of the tumor; however, even mature teratomas can be devastating in the neonatal period because they can interfere with the most critical period of brain development. Due to their midline location, resection may be difficult.

Imaging typically reveals a heterogenous mixture of solid and cystic components, mineralization, and fatty tissue. The solid components and the rim of the cystic regions usually are contrast-enhancing. The mainstay of treatment of teratomas remains maximal surgical resection. Mature teratomas are not sensitive to chemotherapy, but chemotherapy may be beneficial for immature teratomas.[14] Unfortunately, the prognosis remains dismal for infants. Radiation typically is avoided in this age due to long-term effect on neurodevelopmental outcome and because doses of radiation needed to treat mature teratoma are not feasible, particularly in the CNS. Overall survival rates have been reported to be less than 10% at 1 year,[3,15] often because the tumor is very extensive at the time of presentation.

Astrocytomas

Astrocytomas are the most common brain tumor overall in both adults and children; however, they are less common in infants. Most pediatric astrocytomas are low-grade glioma (LGG) (World Health Organization [WHO] grades I and II), with only approximately 10% high-grade glioma (HGG) (WHO grades III and IV). Conversely, a recent review revealed that a majority of neonatal cases were high grade. In a review of 101 cases, Isaacs[16] found that the majority of tumors in this age range were HGGs (55% HGG vs 45% LGG), with the majority glioblastoma multiforme (GBM) (44.6%), a WHO grade IV tumor. Other studies have reported a much lower percentage of GBM among neonatal brain tumors.[17] HGGs in children can be associated with Li-Fraumeni syndrome (inherited *TP53* mutation [**Table 1**]), and LGGs can occur in association with neurofibromatosis type 1 or neurofibromatosis type 2.

The most common presenting symptoms are macrocephaly, hydrocephalus, and intracranial hemorrhage.[16] In some cases, astrocytomas also have been found on routine prenatal US, and a majority of these cases were diagnosed in the 3rd trimester. In the Isaacs[16] study of 101 perinatal astrocytomas, 9% of the cases were stillborn and overall survival was reported to be 46.5%.

Children with LGGs often are treated successfully by surgery alone, when feasible, and, in some cases, chemotherapy is added for patients with residual disease. For HGGs, surgery and radiation therapy commonly are used, but the role of chemotherapy is less clear. In the neonatal population, however, surgery remains the mainstay of treatment, regardless of grade. Chemotherapy can be given for LGGs, if necessary, and some patients may get delayed or salvage radiation if they survive beyond infancy. In the case series by Isaacs, the survival rate for neonates with GBM was 50%,[16] which is higher than reported for older children.[18] The survival rate for fetal cases, however, was only 6.5%.[16] Neonatal HGGs may have a better prognosis than their pediatric or adult counterparts,[5,17,19–22] including sporadic cases

Table 1
Common genetic syndromes associated with pediatric brain tumors

Genetic Syndrome and Incidence	Mutation	Type of Brain Tumor	Other Findings
Ataxia telangiectasia 1:20,000–1:100,000	*ATM*	Meningioma	Progressive cerebellar atrophy, telangiectasias, radiosensitivity, immunodeficiency, cancer predisposition
Cowden syndrome 1:250,000	*PTEN*	Dysplastic cerebellar gangliocytoma Glial tumors (gliosarcoma)	Mucocutaneous papillomatous lesions, multiple hamartomas, cancer predisposition
Turcot syndrome	*APC* (FAP) *MLH1, MSH2, MSH6, PMS2* (HNPCC)	MB Glioma	Adenomatous colorectal polyps, colorectal cancer
Gardner syndrome 1:8000	*APC*	MB	Intestinal polyposis, colorectal cancer as well as cancers of small bowel, stomach, pancreas, thyroid, CNS, liver, bile duct, adrenal glands. Dental abnormalities, osteomas, skin fibromas, dermoid tumors
Gorlin syndrome 1:57,000–1:164,000	*PTCH*	MB Meningioma	Eye anomalies, macrocephaly, cleft lip/palate, bridging of the sella, odontogenic keratocysts, dural/falcine calcifications, basal cell carcinoma
Li-Fraumeni 1:5000	*TP53*	Glioma MB CPC	Multiple cancers (adrenocortical carcinomas, sarcomas, breast cancer)
Multiple endocrine neoplasia type 1 1:30,000	*MEN1*	Pituitary adenoma	Pancreas, pituitary, parathyroid tumors, gastrinomas, carcinoid tumors of the duodenum
Familial retinoblastoma	*RB*	Pineoblastoma	Bilateral retinoblastoma, osteosarcoma
von Hippel-Lindau 1:36,000	*VHL*	Hemangioblastoma	Multiple tumors, (renal angiomas, clear cell renal cell carcinomas; pheochromocytomas, serous cystadenomas, endolymphatic sac tumors)

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Table 1
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Genetic Syndrome and Incidence	Mutation	Type of Brain Tumor	Other Findings
Neurofibromatosis type 1 1:2500–1:3000	*NF1*	Gliomas	Multiple CNS and peripheral nervous system tumors (schwannomas, neurofibromas); vascular dysplasias (moyamoya, stenosis), café au lait spots
Neurofibromatosis type 2 1:33,000–1:37,000	*NF2*	Bilateral vestibular schwannomas Meningiomas Ependymomas	Café au lait spots
Tuberous sclerosis 1:6000–1:10,000	*TSC1/TSC2*	Subependymal giant cell astrocytomas	CNS subependymal nodules, cortical tubers, white matter changes. Cardiac rhabdomyomas, ash leave macules. Benign hamartomas in multiple organs
Rhabdoid tumor predisposition syndrome <1:1000000	*SMARCB1, SMARCA4*	AT/RTs	Extracranial rhabdoid tumors often before age 3 y
Aicardi syndrome 1:100000–1:167000	unknown	Choroid plexus tumors	Infantile spasms, agenesis of corpus callosum, chorioretinal abnormalities

of spontaneous resolution.[23,24] This suggests a difference in underlying biology. Some reports suggest a lower mutational burden in congenital high-grade tumors compared with those in older children.[23,25,26] Many pediatric HGGs are characterized by histone *H3F3A* mutations (H3K27 M or H3.3G34 R/V) or *PDGFRA* amplifications as well as amplifications in *EGFR*, *MYC*, *MYCN*, and *MDM4*.[27] Chromosomal aberrations include 1q gain and, less frequently, 7q gain and 10q loss. In a recent study of HGG in very young children,[26] focal amplifications of *PDGFRA* and *EGFR* were absent and histone H3F3A K27 M mutation was present in only 2 cases (6%), whereas *CDKN2A* amplifications were seen in 2 children. In this study, 1q gain and 10q loss were seen as well. In a separate study of 11 very young infants, Paugh and colleagues[28] reported absence of 1q gain and only 1 case of 10q loss. Some infant HGGs also demonstrate loss of *SNORD,* the gene encoding small nucleolar RNA.[26,27] Additionally, infant HGGs can display recurrent fusion of the kinase domain of NTRK1-3, which typically is not seen in older pediatric HGGs, and may be targetable given the availability of novel NTRK-targeting agents.[22,29,30]

Unfortunately, even with improved surgical techniques and less radiation, neonates with HGG are at increased risk of long-term effects. Seizures, developmental delay, neurocognitive dysfunction, motor disability, and endocrinopathies are common. The Children's Cancer Group CCG-945 study was a phase III trial from 1985 to 1992 that evaluated chemotherapy in children with HGG under 6 years of age with

radiation avoidance for those less than 3 years of age and with radiation for those between ages 3 and 6. Children older than 3 years were randomized to either receive pCV (prednisone, lomustine, and vincristine) or an 8-drugs-in-1-day (8-in-1) regimen (lomustine, vincristine, hydroxyurea, procarbazine, cisplatin, cytosine arabinoside, methylprednisolone, and dacarbazine), and those younger than 3 years old were nonrandomly assigned to the 8-in-1 chemotherapy arm. Despite avoidance of radiation, study survivors diagnosed before 3 years of age had lower IQ, lower visual memory, slower processing speed, and poorer visual motor integration compared with those diagnosed between 3 years and 6 years of age, although the patient populations were too small for statistical analyses.[25] These findings need to be confirmed in larger cohorts but suggest the insult to critical regions of the brain regardless of cause during the neonatal period may lead to worse late effects compared with older children.

Subependymal giant cell astrocytomas (SEGAs) are a unique group of astrocytomas that usually occur in children with tuberous sclerosis complex (TSC) in their first or second decade of life, but, rarely, they may present in neonates. TSC is an autosomal dominant condition that arises as a result of mutations in either the *TSC1* (encoding hamartin) or the *TSC2* (encoding tuberin) gene and typically is characterized by hamartomas in the brain, skin, heart, liver, lung, and kidneys. Under normal circumstances, hamartin and tuberin negatively regulate the mTORC1 complex (mTOR = mammalian target of rapamycin) by preventing substrate use in unfavorable conditions. In patients with *TSC1* and/or *TSC2* mutations, however, this complex is hyperactivated, leading to a downstream kinase signaling cascade that subsequently leads to cell-cycle progression, transcription, translation, and, ultimately, hamartoma formation.[31] Neonates with TSC often present with cardiac rhabdomyomas, causing outflow obstruction as well as arrhythmias, rather than neurologic symptoms from SEGAs. A study from Kotulska and colleagues[32] identified 2.2% of patients with TSC who developed congenital SEGAs. Other common manifestations of TSC include seizures, developmental delay, skin lesions, and extra-CNS hamartomas. On US, SEGAs often appear as echogenic subependymal nodules along the ventricles. They also can have intratumoral calcifications. Treatment of SEGAs have come a long way since the discovery of mTOR inhibitors, with patients showing excellent long-term response. In a multicenter retrospective study by Saffari and colleagues,[33] the mTOR inhibitor everolimus was found to be safe and efficacious for patients under 2 years of age with TSC.

Choroid Plexus Tumors

Tumors developing from the epithelial lining of the choroid plexus of the ventricles are called choroid plexus tumors. They can be CPPs or choroid plexus carcinomas (CPCs). Choroid plexus tumors can be associated with Aicardi syndrome, an X-linked syndrome, characterized by agenesis of corpus callosum, chorioretinitis, and spasms, or with Li-Fraumeni syndrome, characterized by predisposition to multiple tumors secondary to *TP53* mutation. Although papillomas usually are surgically resectable and have a good prognosis, carcinomas have an extremely poor outcome. There is a third group of tumors identified by the WHO called atypical CPPs, which have an intermediate prognosis. Choroid plexus tumors in general are rare (0.4%–0.6% of all pediatric brain tumors) and often occur in infancy (approximately 50% in the first year of life). Most choroid plexus tumors are CPPs, accounting for 10% to 20% of neonatal brain tumors,[1,34] although some reports suggest this number could be higher.[35] Due to their location often associated with or adjacent to the ventricular surface, they often lead to ventriculomegaly and hydrocephalus from overproduction of CSF and blocked drainage. Although papillomas have a very good outcome with surgical resection alone in pediatric patients, in general, there is a significant surgical risk of hemorrhage

and poor outcome in neonates due to immature brain and fragile vascularity. Recently, embolization prior to resection has led to improved surgical outcomes. In some cases, atypical papillomas are treated with neoadjuvant chemotherapy to decrease tumor vascularity and increase the chance of maximal surgical resection.[36] Occasionally, these tumors become very large and lead to massive ventriculomegaly and cortical atrophy.

Choroid plexus tumors typically are detected near the end of the third trimester on fetal US. They appear as fine nodular lesions in the lateral ventricles and modern imaging modalities usually can discriminate them from intracranial hemorrhage. CT scans typically show a large isodense to hyperdense mass with well demarcated margins and avid contrast enhancement.[10] MRI may show a well delineated T1 isointense and T2 hyperintense mass with frondlike appearance and contrast enhancement (**Fig. 2**).

CPCs have a much worse outcome compared with CPPs. These highly invasive tumors can metastasize along the neuroaxis with leptomeningeal spread and, rarely, extracranially into the lungs or abdomen.[15] CPCs also are characterized by frequent *TP53* mutations, which can be somatic (approximately 60% of the cases) or germline and associate with Li-Fraumeni syndrome in approximately 24% of cases[36] (see **Table 1**).

Embryonal Tumors

Embryonal tumors are derived from undifferentiated or poorly differentiated neuroepithelial cells and include MBs, which are common among older children, as well as tumors seen more commonly in the neonatal age group, including atypical teratoid/rhabdoid tumors (AT/RTs) and embryonal tumors with multilayered rosettes (ETMRs) (**Fig. 3**).

Medulloblastoma

MBs are the most common malignant brain tumor of childhood but are less common in neonates. Histologically, they are classified into classic, desmoplastic/nodular, or large cell/anaplastic variants. These are composed of small round blue cells often with Homer-Wright pseudorosettes, necrosis, and increased mitotic activity. In general, classic histology is associated with intermediate prognosis, desmoplastic with

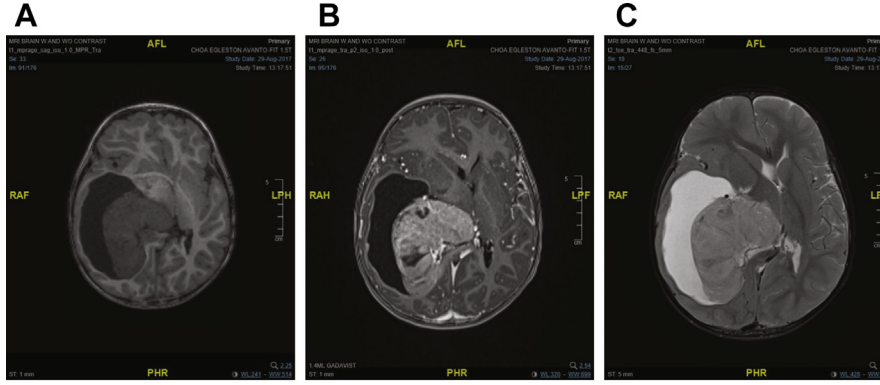

Fig. 2. Infant brain MRIs: (*A*) axial noncontrast T1, (*B*) axial postcontrast T1, and (*C*) axial noncontrast T2 demonstrating the T1/T2 isointense contrast-enhancing CPC arising from the right posterior lateral ventricle.

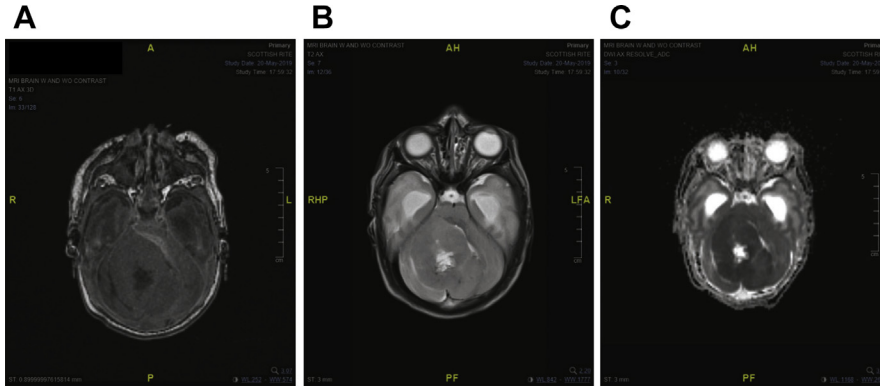

Fig. 3. (*A*) Axial noncontrast T1, (*B*) axial noncontrast T2, and (*C*) axial diffusion-weighted MRIs of infant brain with embryonal tumor, not otherwise specified.

good prognosis and large cell/anaplastic with bad prognosis.[37] More recently, MB has been divided into 4 different molecular subgroups that have implications for prognosis. These include WNT Wingless-type (WNT), the most favorable subtype; Sonic hedgehog (SHH), an intermediate prognosis group (the most common subtype in infants); group 3, which carries the worst prognosis; and group 4, which also has an intermediate prognosis.[38] These highly aggressive tumors are usually treated with a combination of surgery, radiation, and chemotherapy. In neonates and young infants, high-dose chemotherapy with autologous stem cell rescue often is used in lieu of or to delay radiation. Obtaining sufficient numbers of autologous stem cells may be challenging in neonates, however, due to their small size and low blood volume.[39]

MB now is widely accepted to be a tumor exclusive to the posterior fossa. On MRI, MBs usually are isointense on T1-weighted and T2-weighted images and slightly hypointense on diffusion-weighted imaging. They can spread along the neuroaxis requiring spine imaging and lumbar cytology at diagnosis. Prognosis for infant MB has improved with combinatorial approaches to therapy. Prior to the era of high-dose chemotherapy with autologous stem cell rescue, infants with MB had a survival rate of approximately 44% at 12 months.[19] The recently concluded Head Start III trial revealed a 5-year overall survival of 46% $\pm$ 5% for all patients, whereas for infants with desmoplastic histology, the 5-year overall and event-free survival rates were greater than 80%.[40]

Although most cases are sporadic, SHH-driven MBs can be associated with Gorlin syndrome characterized by mutation in *PTCH1* gene and development of skin cancers along with MB (see **Table 1**). Some SHH- MBs also are associated with Li-Fraumeni syndrome. WNT-MBs can be associated with Gardner syndrome, an autosomal dominant disorder characterized by intestinal polyposis and colorectal adenocarcinoma due to mutation in the *APC* gene.

Atypical teratoid/rhabdoid tumors

AT/RTs are rare tumors that disproportionately affect young children. Classically they are characterized by loss of INI1, a member of the SWI/SNF chromatin remodeling complex. Those with germline mutations in the *SMARCB1* (encoding INI1) or *SMARCA4* (encoding BRG1) genes, that is, those with rhabdoid tumor predisposition syndrome, tend to develop AT/RTs earlier in life,[41] even as early as the neonatal period (see **Table 1**). AT/RTs genetically are relatively silent tumors, although recently they have been subclassified into at least 3 different molecular subgroups.[42,43] Primarily

located in the supratentorial compartment, AT/RTs are characterized by a rapidly growing large heterogenous solid and cystic mass with necrosis, mineralization, and hemorrhage. They also can occur in the infratentorium, including the cerebellum, brainstem, cerebellopontine angle, or the spinal cord. CNS dissemination is present at diagnosis in approximately one-third of the cases. AT/RTs are treated similar to MBs with a combination of surgery, high-dose chemotherapy, and radiation if children are older. Prognosis has improved with multimodal therapy, although median survival in the infant age group still is only approximately 9 months.[19,44–46]

Embryonal tumors with multilayered rosettes

ETMRs are another extremely rare group of brain tumors occurring primarily in young infants. Molecularly, these tumors are characterized by amplification of the chromosome 19q region C19 MC coding for a miRNA cluster as well as overexpression of the protein LIN28 A. Histology demonstrates high cellularity with abundant neuropil and cells arranged around vessels forming rosettes (**Fig. 4**). Most of these occur in the first 2 years of life, and approximately two-thirds are supratentorial. Like other embryonal tumors, these often can present with CNS metastasis at diagnosis, and they are associated with extremely poor prognosis, with average survival of approximately 12 months.[47]

Because of the need for multimodal therapy, infants with embryonal tumors are at increased risk of neurologic, cognitive, and endocrine toxicities even when they survive. In a study of 27 infants with CNS tumors from St. Jude Children's Research Hospital, a substantial fraction of survivors had audiovisual deficits, speech and cognitive delays, or growth delays; required hormone replacemen; or developed seizure disorders requiring antiepileptics.[21]

Craniopharyngioma

Craniopharyngiomas arise from remnants of Rathke pouch and typically have excellent overall survival in older children; however, they often are associated with significant morbidities. They are divided into papillary and adamantinomatous histologies. The adamantinomatous subtype is the predominant variant and can occur at any age. Conversely, the papillary subtype is seen almost exclusively in adults.[48] On US, they appear as a large intracranial mass in the suprasellar region, often indistinguishable from a teratoma. MRI may help further delineate the tumor and its impact on normal brain parenchyma.

Although rare, craniopharyngiomas in neonates carry a worse prognosis due to limited treatment options in this age group. Because of their location in the neurohypophysis, children may develop long-term endocrinopathies requiring hormone replacement or management of diabetes insipidus. Occasionally, they may have developmental delay and/or seizures. Surgically, tumors less than 6 cm in diameter are considered to be more likely to undergo gross total resection, whereas those greater than 8 cm usually are associated with a poor outcome.[49] Although radiation often is utilized in older children, because of the significant risk of neurocognitive devastation,[50] it is avoided in neonates.

Neuronal and Mixed Neuroglial Tumors

Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are 2 WHO grade I tumors that are very rare, accounting for less than 1% of all pediatric brain tumors. They both, however, are relatively common in neonates. DIGs are seen almost entirely in infants less than 6 months of age and in most cases are considered congenital. They carry a favorable prognosis with surgical resection

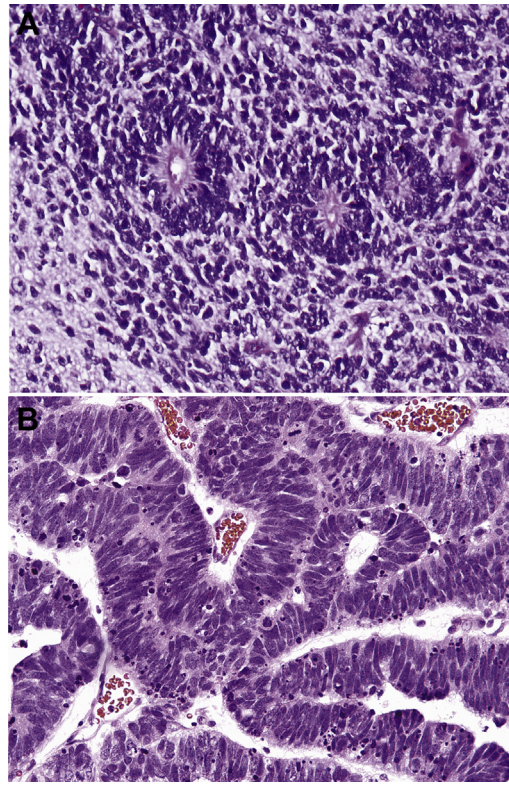

Fig. 4. (*A*) Characteristic pathology of ETMR tumor displaying high cellularity with abundant neuropil and cells arranged around vessels forming rosettes. (*B*) An ETMR tumor displaying medulloepithelioma histology resembling embryonic neural tube with papillary arrangement without obvious multilayered rosettes.

alone. These usually are large cystic supratentorial tumors that can involve the superficial cerebral cortex and leptomeninges. The cysts can grow to massive size with relatively little edema.[10] Multiple lobes commonly are involved with a predilection for frontal and parietal lobes. Rapid head growth with bulging fontanelle are common presenting features. Histologically, both have a stroma rich in collagen and spindle-shaped fibroblastic elements, but DIGs have a prevalence of neuronal elements whereas DIAs have astrocytic components exclusively.[51] On MRI, solid components are T1 and T2 hypointense, whereas the cystic components are classically T1 hypointense but T2 hyperintense.

Treatment primarily is surgical removal. Even with partial resection, long disease-free intervals are achieved without tumor progression. Chemotherapy can be considered in cases of recurrence or growth of residual tumor. Recent studies suggest DIGs may be MAP kinase pathway driven tumors, suggesting a potential role for MEK inhibitors in this disease.[52]

ETHICAL CHALLENGES IN NEONATAL BRAIN TUMOR MANAGEMENT

A brain tumor diagnosis in a neonate presents significant medical and ethical challenges for the medical team, parents, and family. If a diagnosis occurs prenatally,

although still significant, preparations can be made to ensure safe delivery, and consideration given to possible treatment options versus withdrawal of care. If, however, diagnosis is made after birth, the decision process becomes more challenging. One such example is illustrated in **Fig. 5**, where a newborn presented with severe macrocrania at birth and was found to have a large intracranial tumor with minimal residual brain, leaving the family and the medical team with difficult choices. Families frequently are overwhelmed, making it difficult to fully participate in medical decision making. Hospitals without subspecialty care may not be prepared to identify appropriate treatment options, expected side effects, and outcomes or to comment on prognosis.[53] Even when diagnosed at large academic medical centers, accurate prediction of outcomes for intracranial tumors not always is possible. Parents expect clinicians to be knowledgeable experts who can provide objective, evidence-based opinions, but, given the rarity of neonatal tumors, limited data may be available to guide clinicians. Parents also may be asked to make difficult decisions while fatigued, stressed, and grieving. At times, even when the prognosis is expected to be grim, families still may opt to pursue aggressive treatments. Non–tumor-directed therapies, such as hospice and palliative care, are essential when available, as discussed later. Racine and colleagues[54] argue that clinicians may have inherent biases about long-term neurologic outcome that affect their evidence-based prognostication. They suggest a set of 5 practice principles: reflection, humility, open-mindedness, partnership, and engagement. These principles may assist clinicians and help guide their approach in such difficult situations.

An additional issue is the lack of availability of palliative care for neonatal patients. In a recent study, Rosenberg and colleagues[55] found that a palliative care consult was obtained in only 16 of 90 neonates diagnosed with HGG, suggesting an underutilization of palliative care services in the neonatal intensive care unit. The investigators suggest that the reasons may be multifactorial, including a lack of palliative care resources, competing physician and patient priorities, diffusion of responsibility among multiple caregivers, lack of standardized pathways, discomfort among physicians and patients surrounding discussion of these issues, unpredictable timing of disease progression, and lack of patients' awareness of their prognosis.[55]

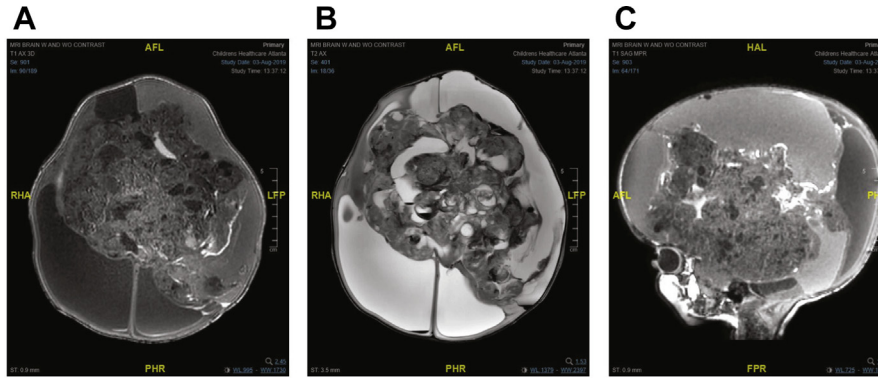

Fig. 5. Illustrative images of a newborn with large intracranial tumor. (*A*) Axial T1, (*B*) axial T2, and (*C*) sagittal MRIs demonstrate very little brain tissue remaining. After a discussion with neurosurgery, neonatology, neuro-oncology, and the family, a decision was made to not intervene. Family chose to enroll in home hospice, where the neonate died peacefully within a few weeks.

GENETIC PREDISPOSITION

There are several rare genetic conditions that predispose to the development of brain tumors[56] (see **Table 1**); however, a majority of these do not present with brain tumors in the neonatal age group. It is essential that neonatologists be aware of these conditions and the potential for brain tumor development to help prepare families for future implications of these genetic diseases.

SUMMARY

Significant research has evaluated the underlying molecular genetic make-up of pediatric brain tumors, with the most recent WHO classification putting more emphasis on molecular characteristics and removing some previously used nomenclature based on histologic architecture alone.[9] Despite advances in understanding and management of pediatric brain tumors, there remains a relative paucity of studies looking specifically at the neonatal population.

This review highlights the most common brain tumors seen in the neonatal population. Neonates are a unique population having a different epidemiologic distribution and tumor biology.[22] Prognosis in general, however, for all neonatal brain tumors remains poor, partly due to the inability of neonates to tolerate significant toxicity that often accompanies treatment regimens, including surgery, chemotherapy, and radiotherapy. With advances in supportive care, innovative therapies, and better diagnostics, this outlook gradually is changing. Key challenges, however, remain. Because of the rarity of these tumors, prospective clinical trials are almost impossible. As a result, clinicians often have to depend on case reports, tumor registries, and clinical experience to guide treatments. Given the lack of prospective clinical data, it is not always clear which patients should receive intervention and whether the toll on future neurocognitive impact is justified. These and other difficult issues make it imperative that, whenever possible, a multidisciplinary team be involved in these rare cases, including neuro-oncologists, neonatologist, neurosurgeons, neurologists, palliative care physicians, and social workers.

Best practices

What is the current practice for neonatal brain tumors?

- Currently, this is not standardized because these are relatively rare. Practice also largely varies based on specific histologic diagnosis (see text).

Best practice/guideline/care path objective(s)

- If diagnosed prenatally, referral may be made to a tertiary care center for anticipated complications during delivery as well as management of the infant.
- If diagnosed at birth, if feasible and safe, the infant should be transferred to a tertiary care center for multidisciplinary care.
- It is important to involve a multidisciplinary team, including neurosurgery, neuro-oncology, neonatology, palliative care, and radiation oncology as well as genetics, social work, and other ancillary services from the outset to consider all options before giving recommendations and to support the family.

What changes in current practice are likely to improve outcomes?

- Early involvement of palliative/supportive care has been shown to improve patient/family satisfaction regardless of outcome.
- Newer therapeutic options, such as targeted therapies, may be better tolerated by neonates as more is learned about the biology of these tumors.

Major recommendations

- Early referral to tertiary care center for multidisciplinary management is strongly encouraged.
- Early involvement of palliative/supportive care team regardless of anticipated outcome is strongly encouraged.
- Improvement in surgical techniques, supportive care, and targeted therapy has led to improvement in outcome for several subtypes of neonatal brain tumors; however, prognosis still remains dismal in general, necessitating the need for more research on this unique patient population and their underlying biological differences.

References/Source(s):[19,51,53]

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