Pediatric Brain Tumors: An Update

Devorah Segal, MD, PhD,[a] and Matthias A. Karajannis, MD, MS[a,b,c]

Brain tumors collectively represent the most common solid tumors in childhood and account for significant morbidity and mortality. Until recently, pediatric brain tumors were diagnosed and classified solely based on histologic criteria, and treatments were chosen empirically. Recent research has greatly enhanced our understanding of the diverse biology of pediatric brain tumors, their molecular and genetic underpinnings, leading to improved diagnostic accuracy and risk stratification, as well as the development of novel biomarkers and molecular targeted therapies. For subsets of patients, these new treatment options have already resulted in improved survival and decreased treatment toxicity. In this article, we provide an overview of the most common childhood brain tumors, describe recent key advances in the field, and discuss the therapeutic challenges that remain.

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Introduction

Brain tumors are rare in childhood but, nevertheless, represent the most common solid tumors in this age group. There are currently more than 4600 tumors of the central nervous system diagnosed annually in the United States in children up to 19 years of age, corresponding to an incidence rate of 5.57 per 100,000.[1] However, 5-year survival rates vary widely with tumor type and have improved greatly with improved surgical and oncologic care. At present, the overall 5-year survival rate for children aged 0–19 years after diagnosis with a CNS tumor is estimated to be 73.6%.[1] Brain tumors in children can present with many different signs and symptoms, largely dependent on the location of the tumor. Headache, nausea, vomiting, and vision loss can be caused by increased intracranial pressure due to obstruction of cerebrospinal fluid flow by tumor growth. Visual field deficits and hormone deficiencies can be presenting signs of suprasellar masses. Ataxia and clumsiness can be caused by posterior fossa tumors, and seizures or personality changes can result from tumors involving cortical areas, particularly in frontal brain regions.[2]

There are currently more than 4,600 tumors of the central nervous system diagnosed annually in the United States in children.

Historically, brain tumors have been classified by their location and histological characteristics, including the apparent cells of origin[3] (Fig 1). The WHO's grading system (Table 1) is based on histologic criteria and is used to determine prognosis, select treatment, and stratify patients for research studies. This classification schema has informed diagnosis and treatment for decades, but current research is rapidly making it less relevant to treatment decisions. Researchers are discovering that the genetic and epigenetic characteristics of a tumor are far more instructive in helping to predict its behavior and choose optimal therapies.[4] This field is still in its infancy, but it carries great promise for revolutionizing care of and outcomes in children with primary brain tumors.

Gliomas

Low-Grade Gliomas (WHO Grades I–II)

Low-grade gliomas, defined as WHO Grades I and II tumors, are a group of astrocytomas that collectively represent the most common brain tumors in children, comprising about 24% of childhood brain tumors.[1] They can be classified based on histology and location, with the WHO grading system based on histological findings

From the [a]Division of Pediatric Hematology/Oncology, Department of Pediatrics, New York, NY; [b]Department of Otolaryngology, NYU Langone Medical Center, New York, NY; and [c]Perlmutter Cancer Center, New York, NY.

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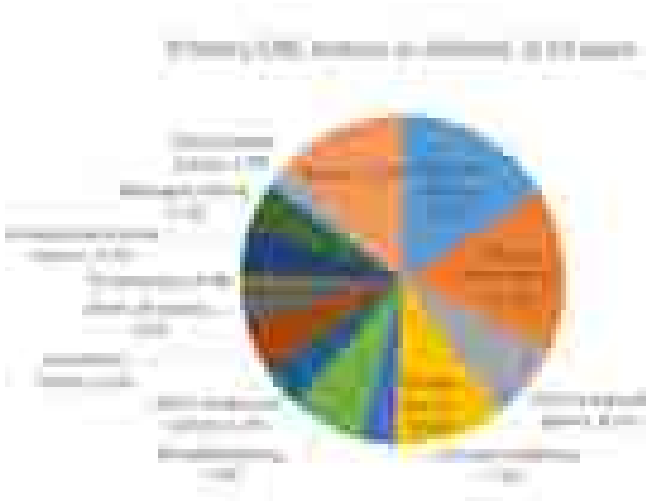

FIG 1. Primary CNS tumors in children (0–19) by histological groupings. *Others include (but are not limited to) lymphomas, choroid plexus tumors, pineal tumors, cranial nerve tumors, and hemangioma. (Adapted with permission from Ostrom et al[1]).

(Table 1). These tumors can arise anywhere in the central nervous system; clinical presentation depends on the tumor location. Two genetic syndromes—neurofibromatosis type I (NF1) and tuberous sclerosis, are associated with a much higher incidence of low-grade gliomas in particular locations. Neurofibromatosis type I carries a greatly increased risk of low-grade gliomas, predominantly in the optic pathway. These tumors often are unresectable due to their location, but those that are partially resected or biopsied are generally consistent with pilocytic astrocytomas. Tuberous sclerosis is associated with subependymal giant cell astrocytomas, which arise almost exclusively in these patients.

Molecular Subtypes

Pilocytic astrocytomas are the most common low-grade gliomas in children. These are defined histologically by the presence of elongated, bipolar astrocytes, and intracellular Rosenthal fibers (Fig 2). NF1 is caused by a mutation in the

TABLE 1. Common pediatric brain tumors (0–19 years) corresponding WHO Grades[3]

	WHO grade	Percentage of all pediatric brain tumors	Typical location	Age (years)	5-Year overall survival
Gliomas				0–19	Varies
Pilocytic astrocytoma	I	15.6	Optic pathway and cerebellum	0–14	97%
Subependymal giant cell astrocytoma	I	*	Ventricles	0–19	Excellent
Pleomorphic xanthastrocytoma	II	<1	Hemispheric and cortically based	0–19	Good
Oligodendroglioma	II	1.1	Supratentorial	15–19	92%
Anaplastic oligodendroglioma	III	0.13	Supratentorial	15–19	Not reported due to rarity
Diffuse astrocytoma	II	4.8	Supratentorial	0–19	83%
Anaplastic astrocytoma	III	1.5	Supratentorial	0–19	32%
Glioblastoma	IV	2.9	Supratentorial	0–19	18%
Ependymal tumors				0–19	75%
Subependymoma	I	Very rare	Fourth ventricle (lateral ventricles less common)	>5	Excellent
Myxopapillary ependymoma	I	Rare	Lower spinal cord	>5	Very good
Ependymoma	II	4–5	Posterior fossa	<6	Good
Anaplastic ependymoma	III	3-4	Supratentorial	<5	Poor
Embryonal tumors				0–4	62%
Medulloblastoma	IV	7.3	Cerebellum	0–14	Varies
Primitive neuroectodermal tumor	IV	1.6	Supratentorial	0–4	Poor
Atypical teratoid/rhabdoid tumor	IV	1.6	Supratentorial	0–4	Poor

***Subtypes not broken down in Central Brain Tumor Registry of the United States (CBTRUS) report.[1]**