High-Grade Gliomas in Children

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KEYWORDS

• Glioblastoma multiforme • Anaplastic astrocytoma • Pediatric brain tumors • Radiation therapy • Chemotherapy

KEY POINTS

- High-grade gliomas include anaplastic astrocytomas and glioblastomas. They account for 3% to 7% of primary brain tumors in children and peak in incidence during adolescence.
- Molecular mutations seen in pediatric glioblastoma multiforme and AAs include p53, PTEN, and LOH at 10q23. p53 and PTEN are associated with a poor prognosis.
- The goals of surgery include pathologic diagnosis and/or gross total resection. Longer progression-free survival is associated with a greater extent of resection.
- In children older than 3 years, chemotherapy plus radiation after surgery is the standard of care. In children younger than 3 years, radiation is associated with significant neurologic morbidity and should be used only when necessary.

INTRODUCTION

Gliomas are primary brain tumors derived from astrocytes and oligodendroglia and are historically separated into low- or high-grade categories according to the World Health Organization (WHO) classification system. Low-grade astrocytomas (WHO grade I and II) are approximately 40% of primary supratentorial tumors of childhood and are more common than high-grade astrocytomas (WHO grade III and IV).[1] Supratentorial high-grade gliomas (HGGs) are further divided into anaplastic astrocytomas (AAs, WHO grade III), anaplastic oligodendrogliomas (WHO grade III), mixed astrocytic tumors, and glioblastoma multiforme (GBM, WHO grade IV).[2] As expected, survival rates are poor and mortality is highest in patients with malignant astrocytomas.

EPIDEMIOLOGY

HGGs account for between 3% and 7% of newly diagnosed primary brain tumors in children.[3,4] GBM is the most common primary brain tumor in the adult population, but GBMs along with AAs account for only about 20% of pediatric supratentorial brain tumors.[1] In the pediatric population, malignant astrocytomas seem to affect boys and girls equally.[5] The incidence peaks during adolescence, although very young children can also develop malignant astrocytomas.[5]

At present, the only known risk factor associated with developing an HGG is prior radiation therapy.[6] Other rare risk factors include genetic syndromes such as Li-Fraumeni syndrome. This syndrome is characterized by 1 or more cancer occurrences in children, including HGGs.[7,8] Mutations of the p53

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tumor suppressor gene play a key role in tumorigenesis in these patients. Neurofibromatosis type 1 is an autosomal dominant genetic disorder caused by mutations of the neurofibromin gene. The clinical manifestations include cutaneous café au lait spots, neurofibromas in any organ system, optic gliomas, and intracranial HGGs.[9] Turcot syndrome, a disease of DNA mismatch repair characterized by adenomatous colorectal polyps and malignant neuroepithelial tumors, has been associated with HGGs in children.[10,11] Other diseases of constitutional mismatch repair deficiency, specifically expression of the MSH6 mismatch repair gene mutation has been linked to HGG development in children.[12] In addition, there have been case reports of GBM occurring in patients with Ollier disease and Maffucci syndrome, both diseases of cartilaginous dysplasia.[13] However, the significance of the occurrence of these malignancies in these syndromes is unknown.

PATHOLOGY

Histopathology

AAs are highly proliferative mitotically active tumors of glial origin with increased cellularity and cellular atypia. GBMs consist of active poorly differentiated astrocytes with high mitotic activity. These neoplasms are typically heterogeneous with areas of hypervascularity and necrosis. Often the necrotic areas are toward the center of the lesion and surrounded by dense hypervascular tissue. The peripheral zones of both AA and GBM are composed of less dense cellular layers that invade and infiltrate the surrounding brain tissue. Typically this invasion is along white matter tracts, including the anterior and posterior commissures, corpus callosum, fornix, and internal capsule. Infiltrating tumor cells are commonly found many centimeters from the original tumor location.

Molecular Features

The molecular profiles of pediatric and adult HGGs are distinct.[14] Mutations in the *p53* tumor suppressor gene are characteristic features of pediatric GBMs and are associated with a poor prognosis. In a multi-institutional trial, the Children's Cancer Group (CCG) identified *p53* mutations in 40.5% of pediatric HGGs.[15] This same *p53* mutation is only seen in secondary adult GBMs. Secondary GBM refers to HGGs that have arisen from the progression of lower-grade gliomas. p53 overexpression in children is associated with a 5-year progression-free survival (PFS) rate of 17% in comparison with a PFS rate of 44% in patients with low p53 expression.[16,17]

Epidermal growth factor receptor (EGFR),[18] PTEN,[19] and the Ras pathway[20] are activated in most adult GBMs, although these alterations are only present in a subset of pediatric patients. *EGFR* amplification is rare (<10%) in children with GBMs than in adults with GBMs, although positive and elevated EGFR immunoreactivity is seen in 80% of pediatric tumors. The CCG trial reported that 24% of pediatric GBMs and AAs had *PTEN* deletions.[21] Although mutations in *PTEN* are rare in pediatric GBM than in GBM in adults, if present, a poorer prognosis can be expected. LOH at 10q23 is a common abnormality found in 80% of pediatric GBMs.

There are at least 2 molecular subtypes of pediatric GBM.[20] One has activation of the Ras/Akt and MAPK pathways and is associated with a poor clinical prognosis. The other subtype does not have Ras/Akt or MAPK pathway activation and has a much more favorable prognosis. In most adult GBMs, the Ras pathway is activated. In children with GBMs with Ras activation, high expression of CD133, nestin, dlx2, and MELK is also seen.

YB1, a protein involved in brain embryogenesis, is upregulated in 72% of pediatric GBMs.[20] This protein is unique to pediatric GBMs and, when localized to the nucleus, is associated with a poor prognosis. When expressed in the cytoplasm of Ras/Akt-negative GBMs, it was associated with a better outcome. A strong positive association between MIB-1 labeling, patient outcome, and histology has also been found. Mean labeling indices were 19.4 $\pm$ 2.66 for tumors classified as AA versus 32.1 $\pm$ 3.08 for those classified as GBM (P = .0024). The 5-year PFS was 33% $\pm$ 7% in 43 patients whose tumors had MIB-1 indices of less than 18%, 22% $\pm$ 8% in 27 patients whose tumors had indices between 18% and 36%, and 11% $\pm$ 6% in 28 patients whose tumors had indices greater than 36% (P = .003), reflecting a significant inverse correlation between proliferative indices and PFS.[22]

Pediatric AAs are associated with both loss and gain of DNA copy number. The most common gains are on chromosome 5q (40%) and 1q (30%), whereas the most common losses are chromosomes 22q (50%) and 6q, 9q (40%).[23] Losses on 17p have also been reported. A shorter survival time is associated with a gain on the 1q arm.[23] PTEN mutation is rare (8%) in pediatric AA, but if present is associated with poor prognosis.[23] In addition, p53 mutations are present in 95% of pediatric AAs.[24]

Clinical Features

As with many brain tumors, the clinical presentation depends on the anatomic location of