Pediatric Oncology

Nalin Gupta
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Daphne A. Haas-Kogan *Editors*

Pediatric CNS Tumors

Third Edition

Springer

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We dedicate this book to our children
Naya, Kavi
Shabnam, Hrittik, and Tizita
Yonatan, Shira, and Maetal

Preface

Pediatric brain tumors are a tremendous challenge for the treating physician. Their diverse biological behaviors, in the unique context of the developing nervous system, require flexible and tailored treatment plans. In the last 20 years, there has been an exponential increase in our understanding of the molecular and genetic basis of human malignancy. This is particularly true for pediatric tumors such as medulloblastoma, glioma, and neuroblastoma. The challenge for clinicians is using this array of new biologic information in a directed and rational manner to select effective and less toxic therapeutic agents.

As with previous editions, the goal of this textbook is to provide a current, biologically based perspective of the management of central nervous system tumors in children. Rather than present every tumor type in an encyclopedic manner, the common tumor types encountered in clinical practice are presented in the initial chapters. The epidemiology, pathological features, clinical presentation, diagnosis, and treatment are discussed for each tumor type. We have separated high- and low-grade glial tumors into separate chapters, mainly because the management and outcomes for these two broad groups of tumors are very different. Additional molecular and genomic data relevant to several tumor types have been added in this edition. In the final chapters, many of the diagnostic and treatment modalities common to all tumors are discussed with an emphasis on emerging and experimental techniques.

It is recognized that a variety of treatment strategies is utilized by many different practitioners and institutions. For the most part, the general management principles used by the authors, most of whom are at the University of California, San Francisco, are presented in the context of standard therapy. Although this approach may underemphasize other equally valid approaches, we believe that the reader will benefit from a coherent approach to the management of childhood tumors.

The editors acknowledge the contribution of the authors, our colleagues at the University of California, San Francisco, the editorial staff at Springer, and our many mentors in the preparation and assembly of this book.

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Low-Grade Gliomas

1

Anuradha Banerjee and Theodore Nicolaides

Contents

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1.1 Introduction

Astrocytomas are the most common subgroup of central nervous system (CNS) tumors in children. The most frequent histological types are pilocytic and fibrillary astrocytomas, which are considered low-grade astrocytomas. A variety of other, less common glial tumors are also seen in children, including pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma, high-grade gliomas, ganglioglioma and desmoplastic infantile ganglioglioma, astroblastoma, ependymoma, and oligodendroglioma. This chapter focuses on low-grade astrocytomas with an emphasis on infiltrating astrocytoma, cerebellar astrocytoma, optic pathway glioma, and oligodendroglioma.

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1.2 Astrocytomas

1.2.1 Epidemiology

Supratentorial tumors account for approximately 40–60 % of all pediatric brain tumors and are almost twice as common in infants as in older children (Farwell et al. 1977; Dohrmann et al. 1985; Dropcho et al. 1987; Ostrom et al. 2015). The majority of supratentorial tumors are gliomas (astrocytoma, oligodendroglioma, and ependymoma) with the most common subtype, low-grade glioma, accounting for half of these. In contrast to the distribution of gliomas in adults, malignant gliomas account for only 20 % of all childhood supratentorial gliomas.

For the majority of gliomas, the etiology remains unknown. Children with familial cancer predisposition syndromes have an increased risk of developing both low- and high-grade gliomas. Environmental factors, such as parental smoking and residential proximity to electromagnetic field sources, have not been associated with pediatric brain tumors, although parental occupation in the chemical/electrical industry might be associated with an increased risk of astroglial tumors in the offspring (Gold et al. 1993; Rickert 1998). Conversely, prenatal vitamin supplementation in mothers may confer a slight protective effect (Preston-Martin et al. 1998; Vienneau et al. 2015). To date, the only environmental agent clearly implicated in developing glioma is exposure to ionizing radiation, which results in a 2.6-fold increased risk of developing this cancer (Ron et al. 1988). Gliomas are described as a second malignant neoplasm following cranial radiation for medulloblastoma and acute lymphocytic leukemia (Steinbok and Mutat 1999; Tsui et al. 2015). Case reports have implied that radiation-induced mutagen sensitivity of lymphocytes may be associated with an increased risk for glioma (Bondy et al. 2001). Inherited predispositions to glioma may also augment the risk of radiation-associated glioma (Kyritsis et al. 2010).

1.2.1.1 Inherited Predispositions to Glioma

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is associated with an increased risk of intracranial tumors, and approximately 15–20 % of patients with NF1 present with low-grade intracranial tumors. Low-grade gliomas arise in a variety of locations in NF1 patients, but are most commonly located in the optic nerve, optic chiasm, hypothalamus, and/or brainstem. They may also occur within the cerebral hemisphere and cerebellum (Listernick et al. 1999).

The *NF1* gene is located on chromosome 17q and encodes a GTPase-activating protein (GAP), termed neurofibromin (NF1), involved in regulating the ras-p21 signaling pathway. Mutations in the *NF1* gene produce heterogeneous signs and symptoms of the disease including dermatologic manifestations, neurofibromas, ocular and bone abnormalities, and optic pathway gliomas. Loss of neurofibromin function due to bi-allelic loss of *NF1* results in constitutive activation of the Ras/Map kinase signaling pathway and drives tumorigenesis in NF1-associated low-grade glioma (Anderson and Gutmann 2015). This mechanism raises the possibility of therapeutic biologic targeting of components of this signaling pathway with pharmacologic agents. Neurofibromatosis may arise from sporadic mutations in the *NF1* gene or through germline transmission of an established mutation (Gutmann et al. 2000). Proteomic analysis of *NF1*-deficient human and mouse brain tumors has revealed elevated levels of mammalian target of rapamycin (mTOR) activity (discussed in Sect. 1.2.5.4) and its downstream targets associated with protein translation and growth (Dasgupta et al. 2005). Neurofibromin is a GTPase that negatively regulates the G-coupled protein, Ras, whose downstream targets include Akt and mTOR (Dasgupta et al. 2005; Sabatini 2006). Therefore, mTOR may also be an attractive molecular target worth further examination. However, NF1-associated CNS tumors, such as pilocytic astrocytomas, rarely demonstrate

alterations in other known oncogenic genes such as *p53*, *EGFR*, *PDGFR*, and *p21*, and these tumors are considered to be benign (Gutmann et al. 2000; Vinchon et al. 2000).

Tuberous Sclerosis

Tuberous sclerosis is an inherited disorder of the *TSC1* and *TSC2* genes that results in a clinical phenotype of widespread hamartomas that can involve several organ systems. The TSC1 and TSC2 genes encode a protein complex that negatively regulates mTOR, an important regulator of cell proliferation and survival. Patients with tuberous sclerosis have abnormal regulation of mTOR signaling, which can result in the development of subependymal giant cell astrocytoma (SEGA) in 10 % of patients with tuberous sclerosis (Curatolo et al. 2008). SEGA is a low-grade, mixed glioneuronal neoplasm that can result in obstruction of CSF flow and hydrocephalus. Treatment is typically surgical, but recent evidence demonstrates that SEGA in the setting of tuberous sclerosis is sensitive to medical treatment with pharmacologic inhibitors of mTOR (Ouyang et al. 2014; Franz et al. 2006, 2014).

1.2.1.2 World Health Organization Grading

The recent World Health Organization (WHO) classification of CNS tumors organizes astrocytomas into four grades (I–IV) in addition to a histological classification system, based on morphologic features. Low-grade histologies are defined as grade I or II. Grades I and II lesions can be of varying histologies, but the most common WHO grade 1 histology is pilocytic astrocytoma, while diffuse astrocytomas are the most commonly observed WHO grade II histology in pediatric patients. Cerebellar astrocytomas, grades I and II, comprise approximately 70–80 % and 15 % of childhood cases, respectively (Steinbok and Mutat 1999). Experimental evidence suggests that grade I and II cerebellar astrocytomas develop from different precursor cells (Li et al. 2001; Sievert and Fisher 2009). Although the use of the WHO classification system remains in widespread use, the emerging importance of characteristic genetic changes has resulted in proposals to update the classification system to include these findings (Louis et al. 2014).

1.2.2 Pathology

1.2.2.1 Grades I and II Astrocytomas

Pilocytic astrocytoma (PA) is the most common low-grade histology in the first two decades of life. PAs can be found throughout the neuraxis (optic pathway, hypothalamus, cerebral hemisphere, brainstem, and spinal cord), although 80 % are found in the cerebellum (Dirven et al. 1997). PA has variable radiographic appearance; tumors can be well-circumscribed without infiltration of the surrounding brain, but when it occurs as an optic pathway glioma, it can have a more, diffusely infiltrative appearance. These gliomas can infiltrate widely, even extending into the posterior visual cortex. This subtype is discussed in greater detail in Sect. 1.4.

Histologically, PAs exhibit a biphasic pattern of compact, bipolar, highly fibrillated astrocytes, accompanied by Rosenthal fibers alternating with loose-textured microcystic regions of eosinophilic granular astrocytes (Fig. 1.1). Unlike malignant astrocytomas, pleomorphism, mitotic figures, hypercellularity, endothelial proliferation, and necrosis may be present, but this does not indicate malignancy or poor prognosis (Steinbok and Mutat 1999). Local leptomeningeal invasion is apparent in half of all cases and has no prognostic significance (Burger et al. 2000).

Other grade I astrocytoma, glioma, and glioneuronal histologies that are seen in pediatric patients include subependymal giant cell astrocytoma, ganglioglioma, dysembryoplastic infantile ganglioglioma, and dysembryoplastic neuroepithelial tumor (Sievert and Fisher 2009).

Grade II astrocytomas are distinct from pilocytic tumors because of their location, degree of infiltration, and presence of genetic aberrations (Kleihues et al. 1993; Louis et al. 2007). Grossly,

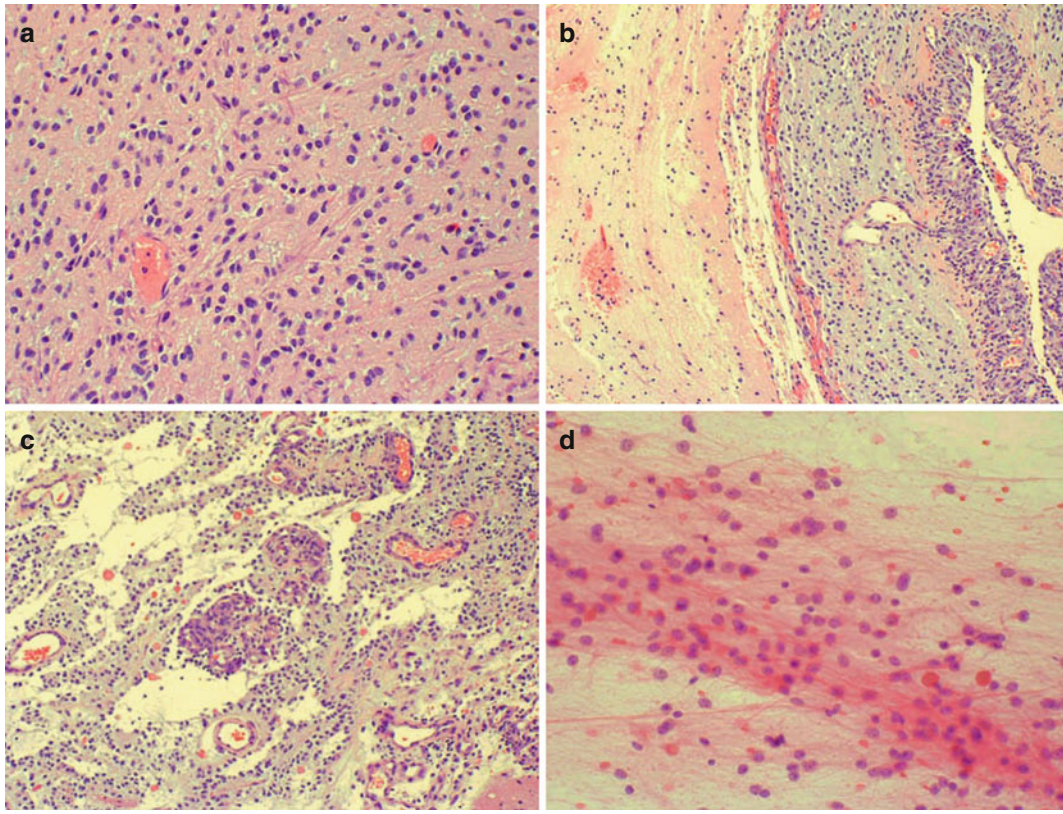

Fig. 1.1 Histopathological features of pilocytic astrocytoma. (**a**) Field of tumor cells demonstrating increased cellularity, mild nuclear atypia, and lack of mitoses. (**b**) Tumor edge with gliotic border (*left* of image) and neovascularization. (**c**) Biphasic pattern of compact, fibrillated astrocytes and loosely textured microcysts with a focus of endothelial proliferation. (**d**) Squash preparations demonstrating thin glial processes ("pili") extending from bipolar tumor cells

grade II astrocytomas are ill-defined lesions that tend to enlarge and distort involved structures. Destruction of brain tissue, however, is more characteristic of higher-grade tumors. Microscopic examination of resected grade II tumor specimens invariably shows diffuse infiltration of the surrounding gray and white matter. Low-power microscopy may show a subtle increase in overall cellularity and disruption of the orderly pattern of glial cells along myelinated fibers. Higher-power examination reveals neoplastic astrocytes with indistinct cytoplasmic features. The diagnosis is often based on the appearance of the nuclei, which are characteristically elongated. Nuclear atypia is minimal in low-grade astrocytomas and mitotic activity is infrequent.

1.2.2.2 Other Low-Grade Subtypes

Low-grade astrocytomas can be further subdivided on the basis of their microscopic appearance. The prognostic value of these subgroups is not entirely clear. Fibrillary astrocytoma is the most common grade II astrocytoma subtype and demonstrates a uniform, compact arrangement of fibrillary astrocytes with varying degrees of cellular atypia on a background of loosely structured tumor matrix (Steinbok and Mutat 1999). Gemistocytic astrocytomas are composed of neoplastic astrocytes with abundant eosinophilic, glial fibrillary acidic protein (GFAP)-positive cytoplasm with nuclei displaced to the periphery (Kaye and Walker 2000). The WHO classification identifies the gemistocytic subtype as low-grade astrocytoma, as long as cellularity and

nuclear atypia remain mild (Louis et al. 2007). The pleomorphic xanthoastrocytoma (PXA), is a rare, GFAP-positive, astrocytic tumor typically occurring in the cerebral hemispheres of children and young adults (Kepes et al. 1973).

Histologically, PXA is characterized by large, neoplastic astrocytes with substantial nuclear pleomorphism and very atypical nuclei. The borders are often infiltrative, and tumor cells may display clustering in an epithelioid fashion (Lindboe et al. 1992; Powell et al. 1996). Desmoplastic infantile astrocytoma (DIA) is a rare tumor occurring in infants 18 months or younger. These tumors are usually large, cystic, supratentorial in location, and have a dural attachment. Histologically, they are loose to dense collagenous stroma with wavy fascicles of spindle cells (Taratuto et al. 1984). The rarest subtype is the protoplasmic astrocytoma, which has prominent microcysts, mucoid degeneration, and a paucity of GFAP positivity (Kaye and Walker 2000). Some consider this a histological pattern of fibrillary astrocytoma, rather than a true variant. Diffuse cerebellar astrocytomas resemble low-grade astrocytomas of the cerebral hemispheres with poorly circumscribed borders and invasion of the surrounding parenchyma. These tumors generally occur in older children, and young adults can undergo malignant transformation (Burger et al. 2000). Regardless of subtype, all low-grade astrocytomas have low cellularity, limited nuclear atypia, and rare mitotic activity. Low-grade astrocytomas with single mitotic figures have prognoses similar to other low-grade tumors (Giannini et al. 1999). A single mitotic figure suggests that the presence of isolated mitoses may not be sufficient to transform an otherwise low-grade astrocytoma to a higher-grade lesion.

1.2.2.3 Biology

Astrocytoma cytogenetic abnormalities occur less frequently and with different patterns in children than in adults (Cheng et al. 1999). In adult low-grade astrocytomas, mutations in the *p53* tumor suppressor gene are common and may herald an early event in malignant progression (Watanabe et al. 1998; Kosel et al. 2001). In contrast, *p53* mutations are not frequently found in the pediatric population (Litofsky et al. 1994; Felix et al. 1995; Ishii et al. 1998). The majority of pediatric pilocytic astrocytomas demonstrate normal cytogenetic findings (Griffin et al. 1988; Karnes et al. 1992; Bigner et al. 1997). In a recent study of 58 pediatric patients, 70% of grade I astrocytomas had a normal cytogenetic profile (Roberts et al. 2001). In another study of 109 pediatric brain tumors, which included 33 low-grade astrocytomas, low-grade astrocytomas mostly showed changes in chromosome copy number (Neumann et al. 1993). Reported cytogenetic abnormalities include gains on chromosomes 1, 7, and 8 and losses of 17p and 17q (White et al. 1995; Wernicke et al. 1997; Zattara-Cannoni et al. 1998).

High-density single-nucleotide polymorphism-based genotyping and comparative genome hybridization (CGH) have revealed duplication or gain in chromosomes 5 and 7, with particular amplification of 7q34 in PA (Pfister et al. 2008; Sievert et al. 2008). Using CGH, *BRAF* was duplicated in 28 of 53 JPAs. In vitro inhibition of BRAF signaling, directly by lentivirus-mediated transduction of BRAF-specific shRNAs or indirectly by pharmacological inhibition of MEK1/2, the immediate downstream target of BRAF, caused G_2/M cell-cycle arrest in astrocytic cell lines (Pfister et al. 2008). The amplification of 7q34 represents a duplication of the *BRAF* gene and fusion with the *KIAA1549* gene. This *BRAF-KIAA1549* fusion results in constitutively activated *BRAF* signaling, with subsequent downstream effects on cell proliferation and survival via *MEK* and *ERK*. The *BRAF-KIAA1549* fusion transcript is detected in the majority of cerebellar pilocytic astrocytomas and less frequently in pilocytic astrocytoma in other locations as well as other low-grade glioma variants. Alternative Ras/Map kinase activating genetic changes have also been described in both pilocytic astrocytoma and other pediatric low-grade glioma histologies. The most common of these is the $BRAF^{V600E}$ mutation, described in 10% of pediatric gliomas, as well as less commonly observed alternate fusion genes involving RAF (Chen and Guttman 2014; Gajjar et al. 2015).

Thus, aberrant activation of the mitogen-activated protein kinase (MAPK) pathway, due to gene duplication or activating mutation of BRAF, is a common event in the tumorigenesis of pediatric low-grade astrocytomas and provides an opportunity for biologically targeted therapies with *BRAF* and/or *MEK* inhibitors.

Constitutive activation of the mTOR pathway is observed in pediatric low-grade glioma, through different mechanisms, in patients who develop either spontaneous or NF1-deficient PA (Dasgupta et al. 2005; Sharma et al. 2005). In tumors with Ras pathway-activating genetic lesions, mTOR, a downstream effector of the Ras pathway, is likely activated by upstream Ras activation (Chen and Guttman 2014). In patients with tuberous sclerosis-associated SEGA, mTOR is shown to be constitutively activated and responsive to treatment with mTOR inhibitors in the clinical setting (Ouyang et al. 2014; Franz et al. 2006, 2014). The identification of these markers may not only direct us to novel molecular targets for drug therapy, but may also allow rapid pathologic characterization and classification of these tumor types.

1.2.3 Clinical Features

Symptoms and signs caused by low-grade gliomas depend on the anatomic location, biological nature of the tumor, and age of the patient. These signs and symptoms may be nonspecific, such as those associated with increased intracranial pressure (ICP), or focal, related to tumor location. Nonspecific symptoms include headache, nausea, and vomiting, subtle developmental delay, and behavioral changes. Some of the behavioral changes associated with slow-growing tumors in children include alterations in personality, irritability, altered psychomotor function, apathy, and declining school performance. It is not uncommon for symptoms to have been present for months or years prior to diagnosis. In infants with open cranial sutures, a tumor may reach a massive size with a gradual increase in head circumference without signs of increased ICP or any other symptoms. Focal symptoms depend upon the location of the tumor and may include hemiparesis, monoparesis, hemisensory loss, dysphasia, aphasia, and impairment of recent memory. Tumors involving the optic pathways can present with quadrantanopia, homonymous hemianopsia, or, in cases with bilateral occipital lobe involvement, cortical blindness. Hemorrhage rarely occurs in low-grade tumors, although one report noted the presence of hemorrhage in 8 % of patients with pilocytic astrocytoma (White et al. 2008).

Epilepsy is a major presenting feature of pediatric patients with brain tumors, and seizures occur in more than 50 % of children with hemispheric tumors (Keles and Berger 2000). The majority of patients with tumor-associated epilepsy harbor slow-growing, indolent neoplasms such as low-grade gliomas. Other relatively slow-growing tumors, for example, astrocytomas, gangliogliomas, and oligodendrogliomas, may also present with a history of generalized seizures. Rapidly growing lesions are more likely to produce complex partial motor or sensory seizures, although generalized tonic-clonic seizures are also common.

1.2.4 Diagnostic Imaging

Magnetic resonance imaging (MRI) and computed tomography (CT) are essential tools in the diagnosis and treatment of brain tumors. Although CT is more commonly available, MRI provides higher sensitivity in differentiating tumor tissue from normal brain, allowing more detailed anatomic characterization of the lesion, and should be obtained in all children with a diagnosis of a brain tumor. A complete series should include the following sequences: T1-weighted axial and coronal (both before and after gadolinium), T2-weighted axial and coronal, and fluid-attenuated inversion recovery (FLAIR). In addition, sagittal plane sequences are helpful in defining anatomy of suprasellar and midline tumors. Other sequences such as fat suppression and MR angiography may also be

required in specific situations. Newer techniques, such as magnetic resonance spectroscopy (MRS), functional MRI, and perfusion measurements, offer the potential of obtaining biochemical and functional information noninvasively (see Chap. 13). It is possible that in the future a pathologic diagnosis may be reached with substantial confidence without the need for open biopsy.

Although low-grade gliomas may produce considerable mass effect upon surrounding structures, neurologic deficits may be minimal. With the exception of pilocytic astrocytoma, low-grade astrocytomas are usually nonenhancing, iso- or hypodense masses on CT scan. Calcification may be detected in 15–20 % of cases, and mild to moderate inhomogeneous contrast enhancement can be seen in up to 40 % of all cases (Lote et al. 1998; Bauman et al. 1999; Roberts et al. 2000; Scott et al. 2002). Some tumors, characteristically PAs, may have cystic changes. On MRI, T1-weighted images show an iso- to hypointense nonenhancing mass that is hyperintense on T2-weighted images. Non-PA low-grade astrocytomas have minimal to no contrast enhancement following gadolinium administration (Fig. 1.2b, d). For this reason, the tumor boundary is difficult to determine with any T1-weighted sequence. FLAIR sequence is very sensitive for defining the extent of tumor infiltration (Fig. 1.2a, c).

Because many low-grade gliomas have a risk of progression or relapse after initial therapy, surveillance MR imaging over time is recommended typically at an interval of 3–6 months, depending on the degree of clinical concern for risk of relapse. In general, for grade II astrocytoma, the two most important features are an increase in the volume of T2-weighted FLAIR signal abnormality and/or new enhancement on post-gadolinium T1-weighted images. These features are also observed in patients who have received radiation treatment, and differentiating tumor recurrence from radiation necrosis continues to present a challenge. Additional information may be obtained from MR spectroscopy and positron emission tomography (PET) scans, but at times, the only method to confirm tumor recurrence is to obtain a surgical biopsy.

1.2.5 Treatment

1.2.5.1 Surgical Indications

A surgical procedure is usually the initial step in the management of low-grade gliomas. The primary objective is to obtain tissue for pathologic diagnosis. A relative exception would be for tumors in locations not amenable to surgery, such as optic pathway/chiasmatic gliomas, although a stereotactic biopsy can safely obtain tissue for histopathologic analysis. The secondary objective is to perform as extensive a resection as possible with acceptable neurologic outcome for the patient. The two variables that must be considered are the extent and timing of resection. Extent of resection is the most important prognostic factor for 5-year overall and progression-free survival (PFS). Patients who have partial resections or residual disease often recur or experience tumor progression (Shaw and Wisoff 2003; Kim et al. 2014). The feasibility of an open surgical approach depends upon several factors. The most important is the exact location of the tumor. Deep lesions within the basal ganglia, thalamus, motor cortex, or brainstem are usually not amenable to open surgical resection, while tumors in other locations can be accessed through various standard approaches. Other factors that modify the decision to attempt surgical resection are the patient's clinical condition, age, associated hydrocephalus, and the surgeon's assessment of risk of neurologic sequelae.

Timing of resection is a controversial topic, and few conclusive studies have been published to date. There are reports questioning the value of immediate treatment when an imaging study suggests a low-grade glioma, as no definitive evidence exists which demonstrates improvement in long-term survival following early intervention (Cairncross and Laperriere 1989; Recht et al. 1992).

In addition to reducing tumor burden and providing tissue diagnosis, resection permits management of increased ICP, prevention of irreversible neurologic deficits, decompression of adjacent brain structures, and control of seizures (Berger et al. 1991, 1993; Haglund et al.

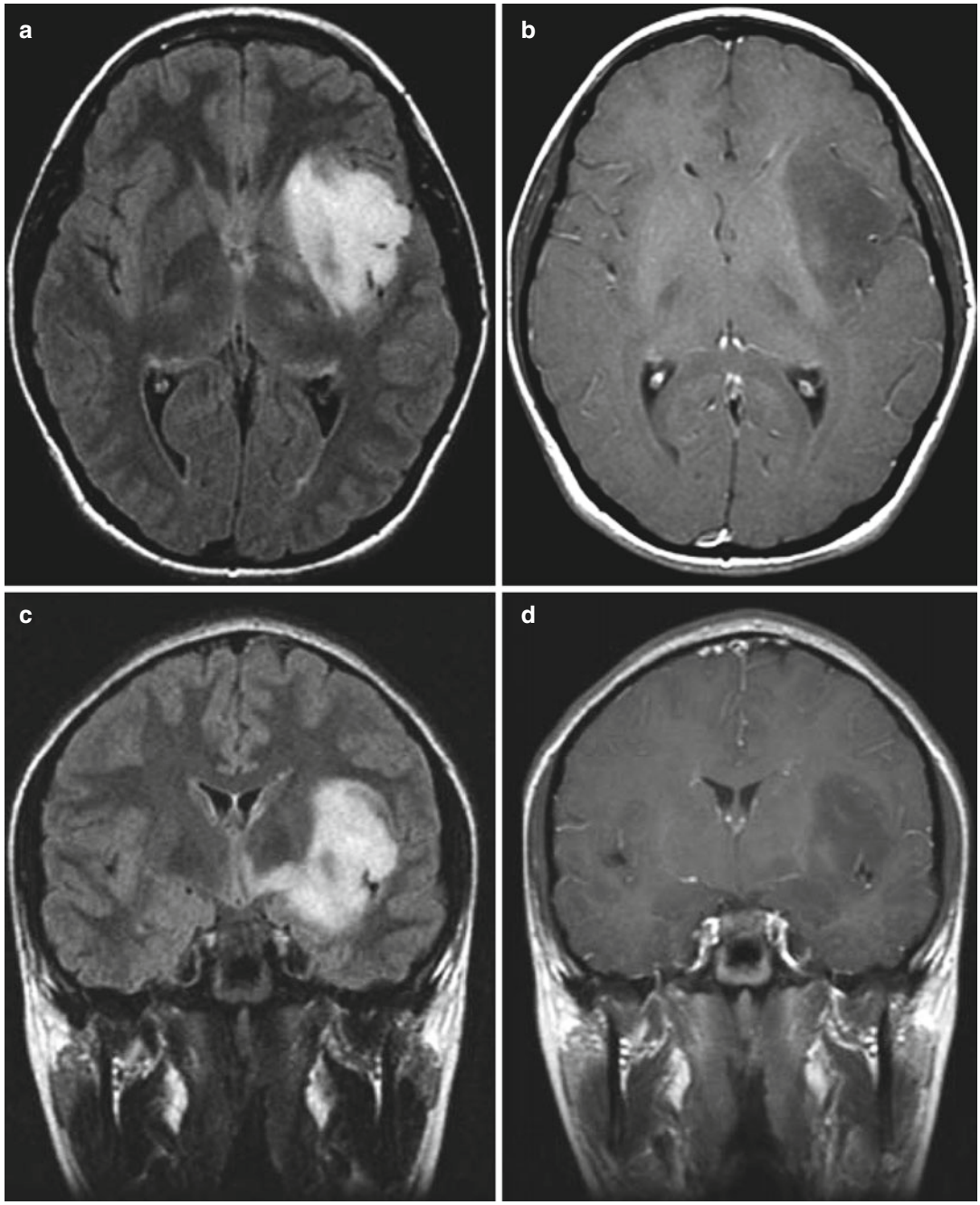

Fig. 1.2 MR images from a teenage girl with a low-grade astrocytoma of the insula who presented with a single seizure. Her neurologic exam was normal. (**a**, **c**) Axial and coronal FLAIR images showing the extent of involvement. Note the tumor infiltration medially under the lentiform nucleus toward the hypothalamus. (**b**, **d**) Corresponding T1-weighted post-gadolinium images showing no appreciable enhancement

1992; Keles and Berger 2000). For patients with discrete JPAs (WHO grade I), gross total resection (GTR), when possible, is curative. Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques enable more extensive resections with less morbidity.

1.2.5.2 Chemotherapy

Although indolent and slow growing, overall 5-year survival rates for patients with diencephalic and hemispheric tumors who have received radiation therapy vary, ranging from 40 % to 70 %. Additionally, the morbidity associated with radiation treatment can be substantial, prompting numerous investigators to explore chemotherapy as an alternative adjuvant treatment to control tumor progression. Chemotherapy effectively provides disease control in many optic pathway tumors (see below) and may improve prognosis for vision maintenance. Studies of early combination chemotherapy regimens with vincristine and actinomycin D, used in children less than 6 years of age, reported 62 % PFS without further therapy; those who did progress did so at a median of 3 years from the start of therapy. The median IQ in this group was 103 (Packer et al. 1988). It is important to recognize that prolonged periods of stable tumor size and clinical symptoms are considered a treatment "response" by many investigators. Alternative combination chemotherapy regimens have also resulted in tumor response in pilot studies. Other drug combinations that have been reported include lomustine and vincristine; 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV); and combinations using cisplatin (Edwards et al. 1980; Gajjar et al. 1993). The combination regimen of carboplatin and vincristine (CV) has been associated with objective response rates (stable disease as well as tumor shrinkage) in the range of 60–70 % (Packer et al. 1997). The combination of TPCV has also been associated with a substantial response rate in a small cohort of patients (Prados et al. 1997).

A large-scale, randomized, phase III, multi-institutional clinical trial conducted by the Children's Oncology Group (COG) examined the relative effectiveness of CV versus TPCV. Four hundred and one children less than 10 years old were enrolled in COG A9952. Of these 401 eligible children, 137 were randomized to receive CV, 137 were randomized to receive TPCV, and 127 patients with NF1 and radiographically verified progressive optic pathway glioma were nonrandomly assigned to the CV arm because of the heightened leukemogenic potential of TPCV in this patient population. Tumor response rates, defined as a decrease in both enhancement and T2 signal on MRI at the end of protocol therapy, were 57 % for CV, non-NF1; 61 % for CV, NF1; and 58 % for TPCV. The 5-year overall survival rates in CV-treated, non-NF1 versus NF1 patients were 86 % and 98 %, respectively. Similarly, 5-year event-free survival (EFS) was improved in NF1 versus non-NF1 patients (69 % vs. 42 %, respectively) and no difference in EFS was found when comparing CV versus TPCV. The median time to progression for CV versus TPCV was 3.2 versus 4.9 years (Ater et al. 2012). A regimen of single-agent vinblastine demonstrated a 3- and 5-year EFS and OS of 43.2 % and 93.2 % (Bouffet et al. 2012). A phase 2 study of bevacizumab and irinotecan in patients with low-grade glioma demonstrated a 2-year PFS of 47.8 % (Gururangan et al. 2014). These findings demonstrate that both therapies can be used successfully to treat low-grade glioma with good overall EFS, thus allowing a delay in radiotherapy.

Although chemotherapy is documented to be active in low-grade glioma, conventional regimens are toxic and provide only transient tumor control. Investigators are exploring the role of mono- and combinatorial therapy to extend treatment response. The HIT-LGG 96 study examined the role of second-line chemotherapy in patients who had disease progression in the chemotherapy arm (94 patients). Of those 94 patients, 27 went on to receive a second round of chemotherapy consisting of vincristine/carboplatin and/or cyclophosphamide regimen, vinblastine alone, temozolomide alone, or other regimen. The median age in this group was 11.8 months. Best achievable response was tumor reduction in 8 patients and stable disease in 13 patients. Thirteen patients recurred 15.7 months after starting second-line chemotherapy. The overall 3-year PFS in the second chemotherapy group was 34 % (Kordes et al. 2008).

A phase II study assessed the efficacy of temozolomide in children with progressive optic pathway glioma and pilocytic astrocytoma. Thirty patients were treated with oral temozolomide for 5 days every 4 weeks. The 2-year PFS and overall

survival rates were 49% and 96%, respectively, with manageable toxicity (Gururangan et al. 2007). These findings illustrate the potential to further delay radiotherapy in this pediatric population by using chemotherapy.

1.2.5.3 Radiation Therapy

As discussed above, low-grade astrocytoma may be curable with GTR. For those patients with unresectable or incompletely resected disease, the use of radiation therapy is controversial. There is some evidence to suggest that while radiation therapy may prolong PFS, it has little impact on overall survival (Pollack et al. 1995). Its use is largely limited to patients with progressive or recurrent disease or in the setting of a highly symptomatic patient who requires tumor stabilization to avert the progression of symptoms. A large-scale multiinstitutional trial, SIOP-LGG 2004, sought to address the role of observation, adjuvant chemotherapy, and radiotherapy in order to assess their optimal therapeutic effect and toxicity on pediatric low-grade glioma after total or subtotal surgical resection. A total of 1,031 patients were enrolled and were nonrandomly assigned to one of three arms in an age-dependent manner. Six hundred sixty-eight patients were assigned to observation only, 216 to vincristine with carboplatin chemotherapy, and 147 to radiation/brachytherapy. Ten-year OS and PFS were 94% and 47%; three quarters of the chemotherapy-treated patients remain unirradiated with 9.3 years of median follow-up (Gnekow et al. 2012). In an 89 patient cohort of pediatric patients treated with conformal radiation for low-grade glioma at St. Jude's Children's Research Hospital, PFS and OS at 10 years were 75.3% and 95.9% (Merchant et al. 2009a, b). Eight-year PFS and OS in a cohort of LGG patients treated with intensity-modulated radiation therapy were 78.2% and 93.7%, with failures largely occurring in the tumor bed (Paulino et al. 2013). For the most part, these studies demonstrate the efficacy of radiation therapy in the treatment of pediatric low-grade gliomas. However, due to concerns about radiation-related side effects, an effort is generally made to delay or forgo radiation in young children.

Because of neurocognitive toxicity associated with radiotherapy, minimizing the dose and radiation fields using stereotactic radiosurgery or proton therapy may provide an effective alternative to standard conformal radiotherapy (Hadjipanayis et al. 2003; Marcus et al. 2005). One prospective trial using stereotactic radiosurgery demonstrated effective control of small, pediatric LGGs that had progressed either after surgery or chemotherapy. The 8-year PFS and overall survival rates using stereotactic radiosurgery in these patients were 65% and 82%, respectively (Marcus et al. 2005). Clinical outcomes using proton therapy in 32 pediatric patients treated for primary low-grade gliomas were comparable to standard radiotherapy. Neurocognitive exams posttreatment appeared stable, with minimal negative changes in working memory and processing speed, except in a subgroup of patients <7 years, who experienced significant declines in full scale IQ, as well as in patients who had significant dose to the left temporal lobe/hippocampus (Greenberger et al. 2014). Proton therapy appears to be safe and equally effective as IMRT or conformal therapy. Alternatively, the use of microsurgery combined with interstitial radiosurgical I-125 seed implantation (IRS) has demonstrated promising results. Nineteen children with low-grade glioma received IRS and/or microsurgery to the tumor site. With a median follow-up of 26 months, 5 tumors had a complete response, 11 tumors had reduction in size, two children developed radionecrosis requiring resection, and one child had progression and died (Peraud et al. 2008). In a cohort of pediatric patients treated with stereotactic brachytherapy, 10-year PFS and OS were 82% and 93%, respectively, again similar to other radiation strategies (Ruge et al. 2011). While this therapy appears feasible, long-term neurocognitive toxicity needs to be assessed.

1.2.5.4 Targeted Molecular Therapy

Overall prognosis and clinical outcome for patients with glioma are associated with tumor grade. Genes associated with glial cell grade and tumorigenesis continue to be identified.

Understanding the pattern of genes activated in glioma will likely provide insight into the natural history and potential clinical course of these tumors and whether they will respond to standard chemotherapeutic regimens or novel molecular targeted therapies. For this reason, the PI3K/Akt/mTOR pathway has been studied in great detail as it plays a large role in the tumorigenesis of many cancers including glial tumors (Sabatini 2006; Guertin and Sabatini 2007).

Two complexes of mTOR exist: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The tumor suppressor genes TSC1/hamartin and TSC2/tuberin are important for the regulation of mTOR activity. Germline mutations of TSC lead to tuberous sclerosis and predisposition to a variety of benign tumors including hamartomas and lymphangioleiomyomas. Many upstream growth factor receptors and PI3K signal through the downstream mediator, mTOR. These observations make mTOR an attractive target for therapeutic intervention (Houghton and Huang 2004).

Further characterization of mTOR's signaling pathway may lead to better application of mTOR inhibitor therapy. Franz et al. used rapamycin, an mTOR inhibitor, to treat 5 TSC patients who had either subependymal giant cell astrocytoma ($n=4$) or pilocytic astrocytoma ($n=1$). In all five cases, tumor regression was observed, and in one case, tumor necrosis occurred (Franz et al. 2006). As reviewed in Sect. 1.2.1.1.2, follow-up studies demonstrated very high response rates of TS-associated SEGA to the mTOR inhibitor everolimus. Based on these observations, as well as the role of mTOR signaling in sporadic and NF1-associated PA as reviewed in Sect. 1.2.2.3, inhibition of mTOR signaling is emerging as a provocative target for treatment of LGGs. In a cohort of 19 recurrent LGG patients treated with a combination of the EGFR inhibitor erlotinib and rapamycin, 1 patient had a partial response to treatment, and 6 patients had stabilization of disease for 12 months or greater (Yalon et al. 2013). A phase 2 study of treatment with everolimus alone in a cohort of 23 patients with recurrent or progressive low-grade glioma observed that 4 subjects had a partial response and 13 subjects had prolonged stable disease (Keiran et al. 2014).

Further exploration of gene expression profiles of grade I and II gliomas have already led to the introduction of novel therapies for pediatric low-grade gliomas. As reviewed in Sect. 1.2.2.3, *BRAF* is strongly implicated in the molecular pathogenesis of pediatric low-grade astrocytoma, and open a new avenue for molecularly targeted agents. In these studies, aberrant MAPK signaling could be inhibited in low-grade astrocytoma cell lines when treated with an inhibitor of the MAPK signaling component MEK. Initial efforts to treat low-grade glioma with the BRAF inhibitor sorafenib were disappointing, with 82 % of patients demonstrating uncharacteristically rapid progressive disease on treatment (Karajannis et al. 2014). Sorafenib was demonstrated to be associated with paradoxical activation of ERK in the setting of a *BRAF-KIAA1549* fusion; hence, the drug may have driven tumor progression in this subset of patients (Sievert et al. 2013). In contrast, pediatric low-grade gliomas with $BRAF^{V600E}$ mutations have a high response rate to $BRAF^{V600E}$-specific inhibitors such as dabrafenib, with 8 out of 15 patients having an objective radiographic response (Kieran et al. 2015). A preliminary report of a phase 1 study of the MEK inhibitor selumetinib (AZD6244) in pediatric low-grade glioma patients was notable for sustained responses in 8 of 38 patients treated, suggesting that MEK inhibition may be a promising therapeutic strategy for these patients (Banerjee et al. 2014), although a larger phase II study is currently underway that will hope to identify by genotype the patients most likely to respond to MEK inhibition. In summary, targeted therapies directed at the Ras/Map kinase pathway have shown significant early promise to treat pediatric low-grade gliomas, but it is still too early to determine which specific inhibitors (BRAF vs MEK) should be used to treat tumors with which particular mutation (*NF1*, *BRAF* fusion, $BRAF^{V600E}$, *RAS*).