Cerebellar Astrocytomas

94

Travis J. Atchley and Jeffrey P. Blount

Contents

Introduction/Overview

Gliomas are the most common CNS tumors in children and comprise 50% of all CNS neoplasms. Low-grade gliomas, specifically juvenile pilocytic astrocytomas (JPAs), are the most common, and the majority occur in the cerebellum. These are associated with stereotypical and often diagnostic radiographic features (Ferris et al. 2017). The current mainstay of treatment of benign cerebellar astrocytomas (CAs) is gross total resection (GTR). Adjunctive therapies such as radiation and chemotherapy can be used in patients with unresectable or recurrent disease or those tumors with more aggressive, undifferentiated histology (Bonfield and Steinbok 2015). Unlike their adult counterparts, low-grade cerebellar gliomas in children have an excellent prognosis, and patients can maintain excellent qualities of life

T. J. Atchley
Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: tatchley@uabmc.edu

J. P. Blount (✉)
Division of Pediatric Neurosurgery, Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: Jeffrey.blount@childrensal.org

C. Di Rocco et al. (eds.), *Textbook of Pediatric Neurosurgery*,
https://doi.org/10.1007/978-3-319-72168-2_90

(Due-Tønnessen et al. 2013; Ogiwara et al. 2012; Pencalet et al. 1999).

This chapter will primarily focus on the presentation, diagnosis, classification, treatment, and prognosis of the most common low-grade CAs.

Epidemiology

Cerebellar astrocytomas (CAs) are tumors of early to mid-childhood (average 6–8 years) and occur with an incidence of 0.4/100,000 persons. They affect boys and girls equally, account for 15–33% of all pediatric CNS tumors, and comprise 25–35% of the posterior fossa (PF) (Johnson et al. 2014). More than one subtype may occur, but the majority show a favorable response to treatment. Juvenile pilocytic astrocytomas (JPAs) are the most common (~70%) and the most benign. These are almost uniformly low grade (WHO grade I) with exceptionally rare malignant transformation. JPAs may occur throughout the neuroaxis; however, they are located in the posterior fossa in approximately 60% of cases. Forty percent are found in the cerebellum and 20% in the brain stem. More aggressive CAs such as pilomyxoid and diffuse astrocytomas (of varying degrees of anaplasia) occur more often in the second decade.

Clinical Presentation

The majority of CAs are benign, slow-growing JPAs which tend to produce progressive symptoms of increased intracranial pressure (ICP). Their predominant location in the posterior fossa predisposes to compression and obstruction of fourth ventricular outflow and the gradual development of obstructive hydrocephalus. Symptom onset is typically gradual initially but may become markedly more acute with advancing degrees of hydrocephalus. Most patients report symptom duration of at least 6 months at time of initial diagnosis. Focal cranial neuropathies are uncommon with the exception of abducens nerve palsies that may accompany hydrocephalus and reflect elevated ICP (Fisher et al. 2008).

By far, headaches are the most common presenting complaint and are seen in over 90% of patients. The classic headache is worst in the morning or during late stages of sleep and is exacerbated with exertion and while recumbent. Headache is due to increased ICP in most cases. Later in the course, patients may develop nausea, vomiting, lethargy, and papilledema which indicates worsening hydrocephalus and increasing ICP.

On examination, patients may exhibit abducens nerve palsies, upgaze limitation, and increased head circumference if presenting prior to 2 years of age (Bonfield and Steinbok 2015; Pencalet et al. 1999). Rarely, patients may present with acute-onset altered mental status or coma.

Cerebellar symptoms, including ataxia, dysmetria, and horizontal nystagmus, are also common but are typically subtle enough to be missed unless specifically evaluated for on examination. These are often mistaken for clumsiness or dyscoordination of normal development (Bonfield and Steinbok 2015).

Imaging and Diagnosis

Appropriate neuroimaging is often diagnostic of CAs, especially JPAs. In the acute setting (e.g., the emergency room), computed tomography (CT) is the modality of choice and illustrates the size of the mass and the presence of hydrocephalus, which is noted in over 90% of cases (Due-Tønnessen et al. 2013; Pencalet et al. 1999). On CT, JPAs typically appear as a cystic mass with an eccentric hypodense, solid (mural) nodule (Fig. 1).

Magnetic resonance imaging (MRI) enables more detailed evaluation of the lesion and its critical relationship to the brainstem and cerebellar peduncles. Characteristically, CAs can be distinguished from other PF tumors such as medulloblastoma, ependymoma, and hemangioblastomas on MRI (Brandão and Young Poussaint 2017). MRI shows T1 hypointensity and T2 hyperintensity of the lesion with consistent contrast enhancement of the mural nodule (Fig. 2). Cyst wall enhancement is variable. If the wall is comprised of gliotic cerebellar tissue, then no enhancement is seen. Thick, irregular enhancement of the

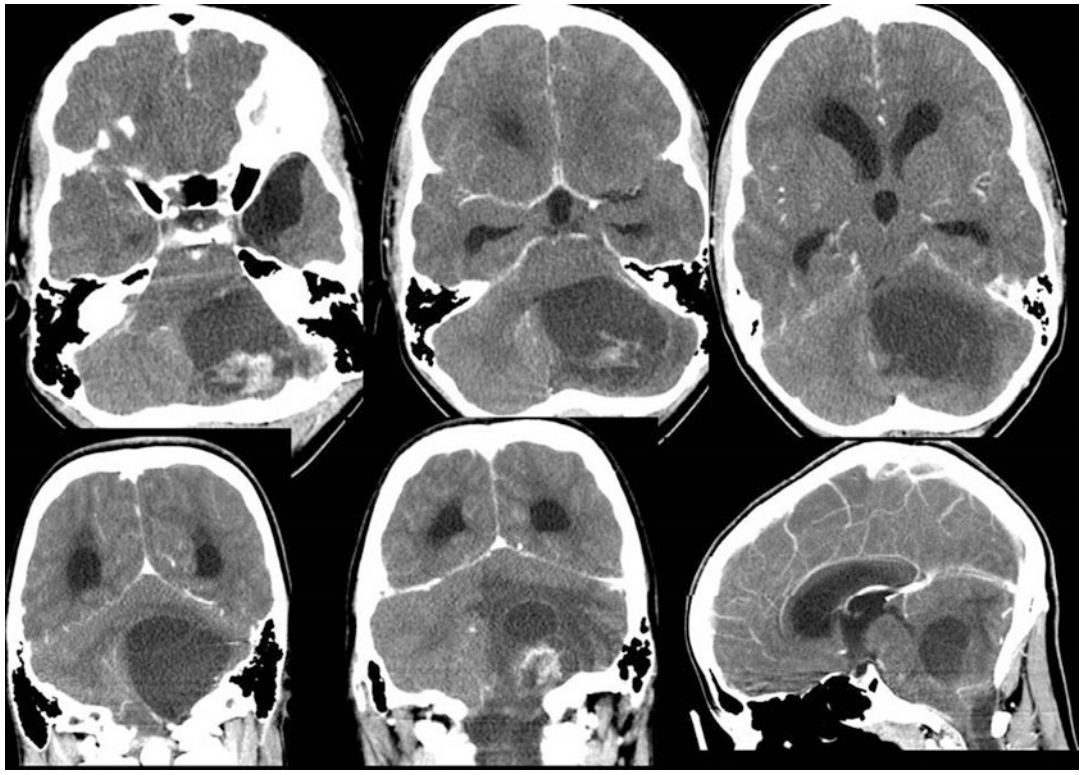

Fig. 1 Computed tomography (CT) findings of posterior fossa cystic lesion with enhancement of mural nodule and significant associated hydrocephalus. (https://www.pedsradiology.com/Imagewindow.aspx?imgname=Uploadimg\81229134775000.jpg&caption=)

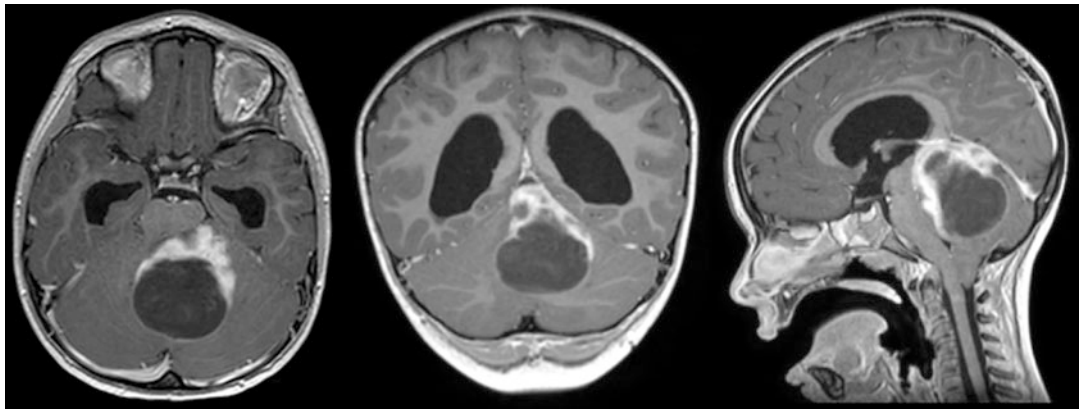

Fig. 2 (Left to right) Axial, coronal, and sagittal post-contrast, T1-weighted MRI of classic JPA with enhancing mural nodule and cystic component

cyst wall may represent intramural tumor, although this is relatively uncommon. Diffusion imaging shows no restriction. Apparent diffusion coefficient (ADC) values may be of benefit in distinguishing JPAs from ependymomas and medulloblastomas, with JPAs having significantly higher ADC values compared to other PF tumors (Rumboldt et al. 2006). Diffuse astrocytomas (DAs) usually show

less consistent enhancement and have more poorly defined borders than lower-grade JPAs. DAs are commonly midline (90%) making it difficult to distinguish from ependymomas or medulloblastomas. In these cases, CT hypodensity, increased diffusivity on MRI, and lack of inositol peak on MR spectroscopy point toward DA versus other PF tumors (Koral et al. 2014).

Recent advances in MRI have utilized vector technology and ADC values to discriminate among the PF tumors with comparable, if not more accurate, results than traditional MRI and MR spectroscopy (Rodriguez Gutierrez et al. 2014). Advances in intraoperative tumor identification with Raman spectroscopy have also shown promise in the ability to accurately diagnose lesions in real time (Leslie et al. 2012).

Classification and Molecular Biology

JPAs are the most common type of CA and make up more than 75% of cases. These are classified as WHO grade I lesions. Grossly, JPAs typically are cystic with a solid component within the wall (mural nodule). The cyst wall may be comprised of neoplastic tissue or cerebellar gliotic tissue. The cystic fluid is usually xanthochromatous. The mural nodule is rubbery and pink-gray in color. Other CAs represent variations on this archetype, including completely solid tumors or cystic tumors without a mural nodule (Bonfield and Steinbok 2015).

Microscopically, the majority of JPAs have alternating (biphasic) patterns of compact fibrillary cells with areas of loose tissue. Rosenthal fibers, thick, eosinophilic bundles of astrocytic processes, may be present (Fig. 3a). JPAs, like other gliomas, stain positive for glial fibrillary acidic protein (GFAP). Pleomorphism, biphasic patterns, hypercellularity, endothelial proliferation, and high mitotic index may be noted but do not usually alter prognosis (Fig. 3b) (Adjei et al. 2008; Ait Khelifa-Gallois et al. 2015). While MIB proliferation index has been found to vary significantly between cystic and solid JPAs, it has not been shown to affect prognosis (Broggini 2012; Horbinski et al. 2010). Some studies have found that >25% oligodendroglial morphology, leptomeningeal invasion, and the absence of degenerative nuclear atypia may portend a poorer outcome (Horbinski et al. 2010).

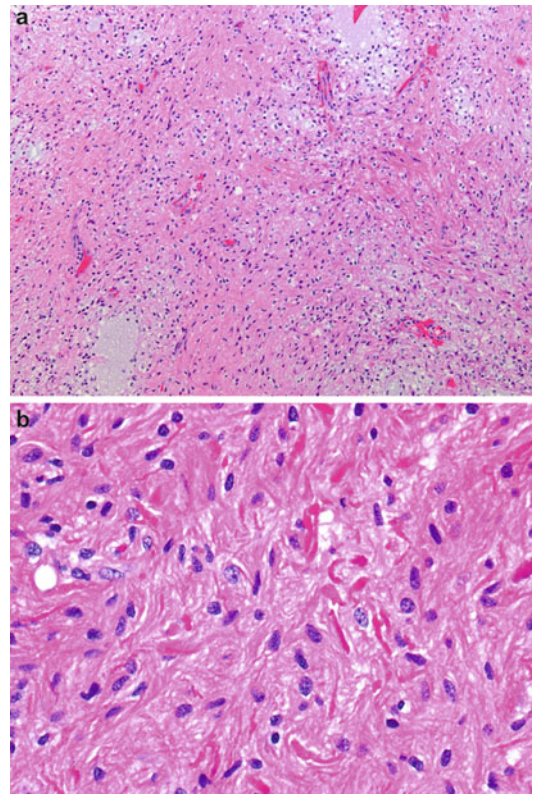

Fig. 3 (**a**) Biphasic morphology of pilocytic astrocytoma, consisting of alternating pattern of cellular and fibrillary areas with loose microcystic zone. (**b**) Photomicrograph (HE, 400x) demonstrates Rosenthal fibers in the cellular, compact component of the tumor. (Photomicrograph courtesy of Rong Li MD, PhD)

Diffuse astrocytomas (DAs) are classified as WHO grade II, with ill-defined borders and more tightly packed, atypical cells. It is unclear if this subtype of CA has an impact on prognosis (Bernhardtsen and Laursen 2003; Conway et al. 1991).

The tumorigenesis of CAs remains unclear. The typical genetic alterations seen in high-grade gliomas, TP53, MGMT methylation, EGFR amplification, etc. are not seen in the low-grade gliomas common to the cerebellum (Ferris et al. 2017; Horbinski et al. 2010; Ilgren and Stiller 1987). The most consistently identified genetic

abnormality in CAs lies on chromosome 7 with duplication at 7q34 resulting in a BRAF fusion gene (Jones et al. 2008). Other aberrations include BRAF point mutations and other BRAF-RAF fusion products. These mutations all alter the MEK/mitogen-activated protein kinase (MAPK) pathway (Jones et al. 2013). Thus, low-grade CAs are often considered a single pathway disease (Ferris et al. 2017; Jones et al. 2008, 2013). Pediatric high-grade gliomas (HGG) share many genetic similarities to adult HGGs. Key differences include mutations in receptor tyrosine kinase PDGFRA, while EGFR mutations are uncommon (Ilgren and Stiller 1987). Additionally, mutations in the RB pathway and TERT enzymes are less common in children (Fisher et al. 2008; Rasheed et al. 1994).

Surgical Intervention

The mainstay of treatment for CAs is surgical resection. The goal is gross total resection (GTR) if safe because CAs are the rare lesion that offers the real possibility of surgical cure. However, the generally benign and indolent behavior of cerebellar tumors allows a reasonable course of subtotal resection and serial observation for those tumors in which radical resection is likely to induce permanent neurologic insult. Many CAs will involute or show highly prolonged clinical and imaging stability such that it is rarely warranted to knowingly induce a lasting neurologic deficit in the initial approach to CAs (Cochrane et al. 1994).

In classic JPA, the mural nodule is the critical target for surgical resection. The cyst wall rarely presents risk for progressive residual disease unless it is unusually thick or nodular and demonstrates enhancement on preoperative MRI (Beni-Adani et al. 2000). Intraoperatively, the surgical findings often supersede imaging when deciding if there is tumor in the cyst wall. Ranges of GTR are reported as 50–89% (Ogiwara et al. 2012; Pencalet et al. 1999; Steinbok et al. 2013). Brainstem and cerebellar peduncle involvement and concern for postoperative neurological deficit are the most common cited barriers to GTR. Surgical discipline should be exhibited in not wandering into critically eloquent structures of the posterior fossa in the pursuit of a CA. Complete resection has been repeatedly found to be the most important prognostic factor for progression-free survival (PFS); however careful judgment is warranted (Kulkarni et al 2013; Rodriguez Gutierrez et al. 2014). Patients with subtotal resections should be considered for reoperation for GTR but only if the operating surgeon is confident of feasibility and safety. Many lesions that involve eloquent regions can be subtotally resected on the initial procedure and followed radiographically. For these lesions a "wait and see" approach is often appropriate in these slow-growing, occasionally spontaneously regressing tumors. Spontaneous postoperative tumor regression has also been reported, and this may represent ischemia from vascular disruption during surgery versus angiogenesis inhibition or apoptotic effect (Steinbok et al. 2006). Recurrence and progression are typically slow, local, and indolent. Limited repeat surgery may be undertaken to address progression and yet preserve neurological function.

The reported 5-year PFS in those with residual tumor ranges from 33% to 65% regardless of residual tumor sizes (Fisher et al. 2008; Ogiwara et al. 2012; Sievert and Fisher 2009). A detailed account of the suboccipital craniotomy for tumor resection is described below.

If there is preoperative hydrocephalus or if there is concern for significant cerebellar swelling intraoperatively, placement of an external ventricular drain (EVD) should be considered. This can be achieved in a separate sterile procedure in the operating room prior to tumor resection. A frontal burr hole over the non-dominant hemisphere, 2–3 cm lateral off midline and 1 cm anterior to the coronal suture, should be drilled. The EVD catheter is tunneled subcutaneously and attached to a closed drainage system within reach of the anesthesia team. Alternatively, an occipital burr hole may be used in the same surgical field as the planned tumor resection. In a fully grown child, the burr hold is made 6 cm superior and 3–4 cm lateral to the inion. In either case, the system is clamped during the formal

operation and opened either prior to durotomy or on an as need basis.

Following induction and intubation, steroids, mannitol, and antibiotics are given. Once EVD placement is complete (if performed), the patient is placed in the Mayfield clamp on the superior temporal line bilaterally. The child is positioned prone on chest and iliac crest rolls. The sitting position is rarely used given the risk of venous air embolism and surgeon fatigue. The neck is flexed in a "military brace" with care to ensure two finger breadths between the chest and chin. The anesthesia team must take special care to maintain proper endotracheal tube position during this process of patient positioning. Hair clipping is performed to surgeon preference.

After usual surgical field preparation, an incision is made from the inion to the spinous process of C2. The midline fascial plane between the paraspinal muscles is dissected with electrocautery. The C2 muscle attachments are left intact unless access to this level is required for entry into the fourth ventricle. A muscle cuff is left at the superior nuchal line for later reattachment of the suboccipital muscles during closure. The dissection should be taken just wider than the width of the foramen magnum for midline approaches and adjusted to either side for off-midline approaches. Care must be taken during subperiosteal dissection along the C1 posterior arch to avoid the vertebral arteries and associated venous plexi. With two paramedian burr holes, the occipital bone is removed in one piece. The posterior arch of C1 is removed with rongeurs, and this enables access to the foramen magnum for CSF egress. Prior to durotomy, the microscope should be draped, preferably at the beginning of the case.

The dura is opened in a Y-shaped fashion, and the sterile microscope is brought into the field. A self-retraction system can be placed, but dynamic retraction should be employed when possible to avoid retraction injury. If the tumor involves the fourth ventricle, vermian disruption should be avoided if possible, but tumor resection should not be compromised by insufficient exposure. STEALTH imaging may be used to determine optimal cortical entry with the shortest distance to the lesion being preferred. Intraoperative ultrasound may also be used to identify the lesion. If tumor is not immediately visible at the cortical surface, a telo-velar approach (or other appropriate route) can be used to access the tumor with as little cerebellar and vermian disruption as possible. The exact etiology of the posterior fossa syndrome (characterized by unremitting postoperative whiny cry, mutism, and difficult to control agitation that persists for weeks to months) is unknown but appears to be triggered by extensive resection or manipulation of the midline vermis.

The shortest route through cortex should be used to approach the lesion. Prior to brain entry, controlling cerebellar swelling and herniation is paramount. Ensure end-tidal CO_2 is appropriate, and the CSF is diverted via EVD, if available. Even so, the cerebellum may appear tense and even herniate through the durotomy. A ventricular needle with a stylet may be used with or without image guidance to drain the tumor cystic component (slowly) if it exists.

During formal tumor resection, a clear demarcation from surrounding parenchyma may be apparent. Suction/bipolar or ultrasonic surgical aspiration can be used for tumor resection. The cyst wall does not have to be removed if it is smooth and non-enhancing on preoperative imaging. However, gross inspection should help guide the surgeon to determine the need for cyst wall resection. In tumors near the fourth ventricle, a cotton patty can be placed along the floor to provide localization and critical protection of brainstem structures. After resection, care inspection of the tumor bed must be performed, and close attention must be paid to the "lip" of the cerebellum beneath retractor blades to prevent small islands of residual tumor.

Pericranium is harvested from the occipital region and sewn into the dural opening. Synthetic dural analogs may also be used, depending on surgeon preference. The bone flap is replaced, and the muscle and fascia are closed along midline The soft tissue and skin are closed in normal fashion, and a sterile dressing is applied.

Postoperatively, patients recover in an intensive care unit (ICU), preferably a specialized neurologic ICU. If present, the EVD is allowed to drain at 10 cm H_2O and is gradually raised over the next few days as tolerated. Steroids should be tapered appropriately. Postoperative imaging is usually obtained within 24 h after surgery, but return for further resection of CAs is less common than for more aggressive posterior fossa masses where outcome more directly correlates with extent of resection. Almost never is it appropriate in a CA to return to surgery for an aggressive take back resection and knowingly induce a lasting neurologic deficit.

Adjunctive Therapies

Recurrent or progressive tumors should be re-resected with the goal of GTR. If this is not possible or if tumors recur despite multiple resections, chemotherapy or radiotherapies may be considered. Response to chemotherapy is variable and unpredictable. While there is no preferred initial chemotherapeutic agent, regimens of carboplatin and vincristine (CV) and of thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine (TPDCV) are commonly used. Both been used with positive results but are complicated by relatively high rates of hypersensitivity and adverse reactions (Ater et al. 2012; Lafay-Cousin et al. 2008; Prados et al. 1997; Ronghe et al. 2010). Ater et al. found that age (>5 years) and amount of residual tumor were independently associated with 5-year event-free survival. They also noted similar tumor response rates (30–35%) with either regimen (Ater et al. 2012). Temozolomide and vinblastine have been trialed as alternative chemotherapeutic agents, but evidence is lacking for their superiority compared to more historical regimens (Bouffet et al. 2012; Gururangan et al. 2007).

Radiotherapy is typically avoided in the treatment of low-grade CAs given the adverse neurocognitive effects and potential for malignant transformation (Abdollahzadeh et al. 1994). Some recent studies have suggested that stereotactic radiosurgery and conformal proton radiotherapy may provide a more feasible treatment alternative; however these remain novel, innovative, yet unproven strategies at this time (Hadjipanayis et al. 2002; Hug et al. 2002). Recently, Cherlow et al. found that conformal radiation therapy led to acceptable progression-free and overall survival rates in 66 patients with unresectable or recurrent JPA (Cherlow et al. 2018). Chemotherapy currently remains the initial adjuvant therapy in recurrent or unresectable CAs, but surgical resection and serial imaging remain the clinical cornerstones of care.

Although CAs usually represent indolent tumors, hydrocephalus is quite common on presentation (over 90% in one series) and requires attention (Due-Tønnessen et al. 2013; Pencalet et al. 1999). Depending on the acuity of presentation and size of cyst cavity, cyst aspiration may provide temporary relief until definitive GTR can be achieved. Alternatively, an external ventricular drain can be placed pre- or intraoperatively for CSF diversion. One series found CSF shunting was requiring in 15% of patients for persistent hydrocephalus despite adequate tumor resection (Due-Tønnessen et al. 2013).

Uncommon Variants

Other low-grade gliomas (LGGs) of the cerebellum exist but are far less common than JPAs (Sridhar et al. 2011). Diffuse or fibrillary histologic subclassifications of LGG have been noted, but no significant clinical or predictive value has been associated with these other subtypes of LGG (Bernhardtsen and Laursen 2003). Pilomyxoid astrocytomas (Fig. 4) may resemble JPAs radiographically, and there is some evidence the two tumors are related genetically (Ge et al. 2011). Other LGGs include pleomorphic xanthoastrocytomas and lipidized glioblastoma multiforme, but these are exceedingly rare in the cerebellum. Regardless of the specific histopathology, almost all cerebellar LGGs are managed with gross total resection, if safe. Like JPAs, adjunctive therapies are only employed in partial/subtotal resection, recurrent, or unresectable

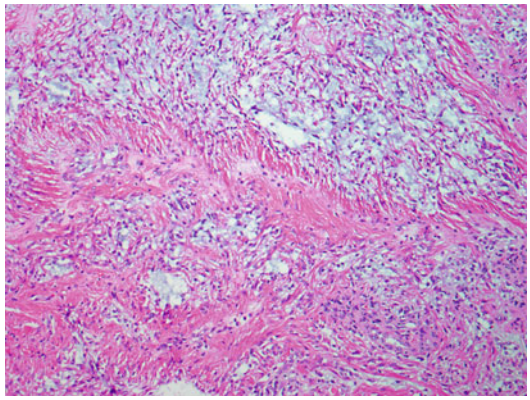

Fig. 4 Photomicrograph (HE 200X) demonstrates prominent angiocentric arrangement of monomorphic bipolar cells with abundant myxoid background matrix characteristic of pilomyxoid astrocytoma. (Photomicrograph courtesy of Rong Li MD, PhD)

cases (Desai et al. 2001; Ge et al. 2011; Kumar et al. 2003).

High-grade gliomas (HGGs) in children are uncommon, representing only 17% of all gliomas in one large study (Qaddoumi et al. 2009). In particular, glioblastoma multiforme (GBM) comprises only 3% of all pediatric CNS tumors (Das et al. 2012). The majority of HGGs occur in the brainstem or supratentorial region. Das et al. reported that only 4.6% of pediatric glioblastomas occur in the cerebellum, and only 25–30 cases of pediatric cerebellar GBM have been reported in the extant literature (Das et al. 2012; Kalina 2012). Unlike low-grade gliomas, HGGs may exhibit a strong male predominance (Das et al. 2012). Unsurprisingly, a shorter duration of symptoms is common given the more aggressive nature of HGGs (Hargrave et al. 2008). Imaging features of high-grade gliomas in children resemble those of adults, including peripheral or irregular enhancement (approximately 80%) with more extensive peritumoral edema than LGGs.

Like LGG, gross total resection is an independent prognostic factor in overall survival. In almost all cerebellar HGGs, adjuvant chemotherapy and radiation are necessary. Since 2005, there has been a gradual shift away from monotherapy with PCV toward oral temozolomide and concomitant radiotherapy (Das et al. 2012; Stupp et al. 2005). Reported survival rates in pediatric GBM range from 13 to 20 months, somewhat better than the reported adult survival of 9–12 months (Das et al. 2012; Perkins et al. 2011; Stupp et al. 2005).

Prognosis and Quality of Life

The prognosis of low-grade CAs remains excellent. The overall mortality rate ranges from 0% to 4% in large studies (Ogiwara et al. 2012; Pencalet et al. 1999). The 25-year survival rates for JPA and solid CAs are greater than 90% and approximately 40%, respectively (Choudhri et al. 2016; Gjerris and Klinken 1978). In a single series, progression-free survival was 75%, and 5-year survival rates were 100% and 92% after GTR and subtotal resection, respectively (Fernandez et al. 2003). Unsurprisingly, partial resection and atypical CA variants, pilomyxoid in particular, were associated with worse prognosis (Fernandez et al. 2003). Long-term data regarding stereotactic radiosurgery and proton radiotherapy for recurrent CAs are currently lacking.

Like survival, postoperative functional outcomes of low-grade CA are good. One series found that over 95% of patients had a normal Barthel index, a measure for activities of daily living (Due-Tønnessen et al. 2013). Quality of life (QOL) scores are similar to the general population, despite some patients sustaining permanent neurologic deficits and emotional complaints. Tumor pathology, hydrocephalus, preoperative symptom duration, surgical resection and complications, and any adjuvant therapies may alter outcome. The incidence of permanent neurologic deficits varies widely, with reported ranges between 15% and 50% (Ait Khelifa-Gallois et al. 2015; Steinbok et al. 2013; Zuzak et al. 2008). Most often, deficits involve cerebellar dysfunction including fine manual skill impairments, gait abnormalities and imbalance, writing difficulties, slowed motor movements, and speech difficulties. In large, vermian lesions, particularly solid CAs, 0–8% of patients may suffer from cerebellar mutism (Due-Tønnessen et al. 2013; Ogiwara et al. 2012; Steinbok et al. 2013). Impairments in cognition are less common, and the vast

majority of patients (over 80%) partake in a normal educational curriculum (Ait Khelifa-Gallois et al. 2015; Steinbok et al. 2013).

Follow-Up and Surveillance

No standard postoperative protocol exists for following patients with low-grade CAs. The use of postoperative imaging and MRI surveillance remains debatable. MRI in children carries its own emotional and medical risks. Children often require general anesthesia for each MRI, and the risks of sedation may outweigh any potential benefit to serial neuroimaging, especially in cases of GTR. It is logical to obtain more frequent surveillance imaging in patients with subtotal resections or those with recurrence despite a GTR. In patients with GTR of low-grade CA, surveillance imaging may only be necessary in cases of suspected recurrence (Vassilyadi et al. 2009).

In one study of patients with GTR, recurrence occurred in 2.9% of patients 6 years after initial resection (Alford et al. 2016). Another study comparing rates of recurrence by location and surgical resection identified recurrence in 5.9% of patients with GTR. Patients with radiographic residual tumor and subtotal resections had recurrence rates of 47.8% and 55.6%, respectively. Tumors with fourth ventricular involvement were most likely to recur. No significant difference in recurrence was noted between JPAs and solid CAs (Ogiwara et al. 2012).

Given the low rates of recurrence in patients with GTR, most centers recommend an initial postoperative MRI at 3–6 months, followed by annual imaging for 5 years, and then decreasing frequency thereafter. Ten years appears to be the most reported and acceptable postoperative surveillance period (Due-Tønnessen et al. 2013; Ogiwara et al. 2012).

Conclusion/Future Directions

Despite advances in radiotherapy and chemotherapy, surgery remains the mainstay of treatment for low-grade CAs. While common BRAF and chromosome 7 gene alterations have been identified, no clinically applicable and safe agent has been developed at this time to specifically treat CAs in lieu of resection. However, continued investigation is underway, and potential regulators/inhibitors of the MEK/MAPK pathway may be developed for clinical practice (Adjei et al. 2008). There is current use of mTOR inhibitors in subependymal giant cell astrocytomas in patients with tuberous sclerosis, and there is promise that these agents may be used in JPAs (Franz et al. 2006). The improved understanding of low-grade CA tumorigenesis has led to using other potential chemotherapeutic agents, including vinblastine, temozolomide, and bevacizumab (Bouffet et al. 2012; Gururangan et al. 2007; Hwang et al. 2013).

Developments in MR technology have also led to improved preoperative identification and classification of CA. Increased accessibility and use of intraoperative Raman spectroscopy may also improve GTR rates and thus outcomes in this population (Leslie et al. 2012).

References

Abdollahzadeh M, Hoffman HJ, Blazer SI, Becker LE, Humphreys RP, Drake JM et al (1994) Benign cerebellar astrocytoma in childhood: experience at the hospital for sick children 1980?1992. Childs Nerv Syst 10:380–383

Adjei AA, Cohen RB, Franklin W, Morris C, Wilson D, Molina JR et al (2008) Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol Off J Am Soc Clin Oncol 26:2139–2146

Ait Khelifa-Gallois N, Laroussinie F, Puget S, Sainte-Rose C, Dellatolas G (2015) Long-term functional outcome of patients with cerebellar pilocytic astrocytoma surgically treated in childhood. Brain Inj 29:366–373

Alford R, Gargan L, Bowers DC, Klesse LJ, Weprin B, Koral K (2016) Postoperative surveillance of pediatric cerebellar pilocytic astrocytoma. J Neuro-Oncol 130:149–154

Ater JL, Zhou T, Holmes E, Mazewski CM, Booth TN, Freyer DR et al (2012) Randomized study of two chemotherapy regimens for treatment of low-grade glioma in Young children: a report from the children's oncology group. J Clin Oncol 30:2641–2647

Beni-Adani L, Gomori M, Spektor S, Constantini S (2000) Cyst wall enhancement in pilocytic astrocytoma:

neoplastic or reactive phenomena. Pediatr Neurosurg 32:234–239
Bernhardtsen T, Laursen H, Bojsen-Miller M, Gjerris F (2003) Sub-classification of low-grade cerebellar astrocytoma: is it clinically meaningful? Childs Nerv Syst 19:729–735
Bonfield CM, Steinbok P (2015) Pediatric cerebellar astrocytoma: a review. Childs Nerv Syst 31:1677–1685
Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M et al (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol Off J Am Soc Clin Oncol 30:1358–1363
Brandão LA, Young Poussaint T (2017) Posterior fossa tumors. Neuroimaging Clin N Am 27:1–37
Broggini M (2012) RAS/RAF/MEK inhibitors in oncology. Curr Med Chem 19:1164–1176
Cherlow JM, Shaw DW, Margraf LR, Bowers DC, Huang J, Fouladi M, et al (2018) Conformal radiation therapy for pediatric patients with low-grade glioma: results from the children's oncology group phase II study XXXX. Int J Radiat Oncol. Available: https://linkinghub.elsevier.com/retrieve/pii/S0360301618339518. Accessed 14 Jan 2019
Choudhri AF, Siddiqui A, Klimo P (2016) Pediatric cerebellar tumors. Magn Reson Imaging Clin N Am 24:811–821
Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JRW (1994) The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg 20:19–29
Conway PD, Oechler HW, Kun LE, Murray KJ (1991) Importance of histologic condition and treatment of pediatric cerebellar astrocytoma. Cancer 67(11): 2772–2775
Das KK, Mehrotra A, Nair AP, Kumar S, Srivastava AK, Sahu RN et al (2012) Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. Childs Nerv Syst 28:2055–2062
Desai KI, Nadkarni TD, Muzumdar DP, Goel A (2001) Prognostic factors for cerebellar astrocytomas in children: a study of 102 cases. Pediatr Neurosurg 35:311–317
Due-Tønnessen BJ, Lundar T, Egge A, Scheie D (2013) Neurosurgical treatment of low-grade cerebellar astrocytoma in children and adolescents: a single consecutive institutional series of 100 patients. J Neurosurg Pediatr 11:245–249
Fernandez C, Figarella-Branger D, Girard N, Bouvier-Labit C, Gouvernet J, Paz Paredes A et al (2003) Pilocytic astrocytomas in children: prognostic factors – a retrospective study of 80 cases. Neurosurgery 53: 544–553.; ; discussion 554–555
Ferris SP, Hofmann JW, Solomon DA, Perry A (2017) Characterization of gliomas: from morphology to molecules. Virchows Arch 471:257–269
Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD et al (2008) Outcome analysis of childhood low-grade astrocytomas. Pediatr Blood Cancer 51:245–250
Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G et al (2006) Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 59:490–498
Freeman CR, Farmer J-P, Montes J (1998) Low-grade astrocytomas in children: evolving management strategies. Int J Radiat Oncol 41:979–987
Ge P, Wang H, Qu L, Chen B, Fu S, Luo Y (2011) Pilomyxoid astrocytoma in cerebellum. Chin J Cancer Res 23:242–244
Gjerris F, Klinken L (1978) Long-term prognosis in children with benign cerebellar astrocytoma. J Neurosurg 49:179–184
Gururangan S, Fisher MJ, Allen JC, Herndon JE, Quinn JA, Reardon DA et al (2007) Temozolomide in children with progressive low-grade glioma. Neuro-Oncol 9:161–168
Hadjipanayis CG, Gardner P, Flickinger JC (2002) Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary. J Neurosurg 97:9
Hargrave D, Chuang N, Bouffet E (2008) Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine glioma. J Neuro-Oncol 86:313–319
Horbinski C, Hamilton RL, Lovell C, Burnham J, Pollack IF (2010) Impact of morphology, MIB-1, p53 and MGMT on outcome in pilocytic astrocytomas. Brain Pathol 20:581–588
Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredo LN et al (2002) Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlenther Onkol 178:10–17
Hwang EI, Jakacki RI, Fisher MJ, Kilburn LB, Horn M, Vezina G et al (2013) Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer 60:776–782
Ilgren EB, Stiller CA (1987) Cerebellar astrocytomas. Part II. Pathologic features indicative of malignancy. Clin Neuropathol 6:201–214
Jennings MT, Sposto R, Boyett JM, Vezina LG, Holmes E, Berger MS et al (2002) Preradiation chemotherapy in primary high-risk brainstem tumors: phase II study CCG-9941 of the children's cancer group. J Clin Oncol 20:3431–3437
Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC et al (2014) Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomark Prev 23:2716–2736
Jones DTW, Kocialkowski S, Liu L, Pearson DM, Bäcklund LM, Ichimura K et al (2008) Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68:8673–8677
Jones DTW, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz H-J et al (2013) Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45:927–932
Kalina P (2012) Pediatric cerebellar hemorrhagic glioblastoma Multiforme. Open Neuroimaging J 6:13–15

Koral K, Alford R, Choudhury N, Mossa-Basha M, Gargan L, Gimi B et al (2014) Applicability of apparent diffusion coefficient ratios in preoperative diagnosis of common pediatric cerebellar tumors across two institutions. Neuroradiology 56:781–788

Kulkarni AV, Piscione J, Shams I, Bouffet E (2013) Long-term quality of life in children treated for posterior fossa brain tumors. J Neurosurg Pediatr 12:235–240

Kumar S, Retnam TM, Menon G, Nair S, Bhattacharya RN, Radhakrishnan VV (2003) Cerebellar hemisphere, an uncommon location for pleomorphic xanthoastrocytoma and lipidized glioblastoma multiformis. Neurol India 51:246–247

Lafay-Cousin L, Sung L, Carret A-S, Hukin J, Wilson B, Johnston DL et al (2008) Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma. Cancer 112:892–899

Leslie DG, Kast RE, Poulik JM, Rabah R, Sood S, Auner GW et al (2012) Identification of pediatric brain neoplasms using Raman spectroscopy. Pediatr Neurosurg 48:109–117

Ogiwara H, Bowman RM, Tomita T (2012) Long-term follow-up of pediatric benign cerebellar Astrocytomas. Neurosurgery 70:40–48

Pencalet P, Maixner W, Sainte-Rose C, Lellouch-Tubiana-A, Cinalli G, Zerah M et al (1999) Benign cerebellar astrocytomas in children. J Neurosurg 90:265–273

Perkins SM, Rubin JB, Leonard JR, Smyth MD, El Naqa I, Michalski JM et al (2011) Glioblastoma in children: a single-institution experience. Int J Radiat Oncol 80:1117–1121

Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA (1997) Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neurooncol 32(3):235–241

Qaddoumi I, Sultan I, Gajjar A (2009) Outcome and prognostic features in pediatric gliomas. Cancer 115:5761–5770

Rasheed BK, McLendon RE, Herndon JE, Friedman HS, Friedman AH, Bigner DD, Bigner SH (1994) Alterations of the TP53 gene in human gliomas. Cancer Res 54(5):1324–1330

Rodriguez Gutierrez D, Awwad A, Meijer L, Manita M, Jaspan T, Dineen RA et al (2014) Metrics and textural features of MRI diffusion to improve classification of pediatric posterior Fossa tumors. Am J Neuroradiol 35:1009–1015

Ronghe M, Hargrave D, Bartels U, Tabori U, Vaidya S, Chandler C et al (2010) Vincristine and carboplatin chemotherapy for unresectable and/or recurrent low-grade astrocytoma of the brainstem. Pediatr Blood Cancer 55:471–477

Rumboldt Z, Camacho DLA, Lake D, Welsh CT, Castillo M (2006) Apparent diffusion coefficients for differentiation of cerebellar tumors in children. Am J Neuroradiol 27:1362–1369

Sievert AJ, Fisher MJ (2009) Pediatric low-grade gliomas. J Child Neurol 24:1397–1408

Sridhar K, Sridhar R, Venkatprasanna G (2011) Management of posterior fossa gliomas in children. J Pediatr Neurosci 6:S72–S77

Steinbok P, Poskitt K, Hendson G (2006) Spontaneous regression of cerebellar astrocytoma after subtotal resection. Childs Nerv Syst 22:572–576

Steinbok P, Mangat JS, Kerr JM, Sargent M, Suryaningtyas W, Singhal A et al (2013) Neurological morbidity of surgical resection of pediatric cerebellar astrocytomas. Childs Nerv Syst 29:1269–1275

Stupp R, Weller M, Belanger K, Bogdahn U, Ludwin SK, Lacombe D et al (2005) Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med 352(10):987

Vassilyadi M, Shamji MF, Tataryn Z, Keene D, Ventureyra E (2009) Postoperative surveillance magnetic resonance imaging for cerebellar astrocytoma. Can J Neurol Sci 36:707–712

Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA (2008) Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. Childs Nerv Syst 24:1447–1455