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SPECIAL ANNUAL ISSUE

Pediatric cerebellar astrocytoma: a review

Christopher M. Bonfield[1] · **Paul Steinbok**[1]

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Abstract
Introduction Cerebellar astrocytomas (CA) are one of the most common posterior fossa tumors in children. The vast majority is low grade, and prognosis for long-term survival is excellent.
Methods Recent literature about CA was reviewed to provide an up to date overview of the epidemiology, pathology, molecular and cell biology, diagnosis, presentation, management, and long-term outcomes.
Results Surgical resection remains the first-line treatment with complete removal of the tumor the goal. However, even when only subtotal resection has been achieved, there is a significant chance that the tumor will remain stable or will regress spontaneously. Adjuvant chemotherapy is reserved for those tumors that progress despite surgery, and more personalized chemotherapy is being pursued with better understanding of the molecular genetics of this tumor. Radiotherapy has generally not been recommended, but stereotactic radiotherapy and conformal proton beam radiotherapy may be reasonable options in the setting of relapse or progression. In the long term, permanent neurologic deficits, mainly cerebellar dysfunction, are common, but quality of life and cognitive function are generally good.
Conclusions Low-grade CA remains primarily a surgical disease, with excellent survival rates. Care must be taken with surgery and adjuvant treatments to preserve neurologic function to allow for optimal outcomes in the long term.

✉ Christopher M. Bonfield
bonfieldcm@gmail.com

[1] Division of Neurosurgery, Department of Surgery, BC Children's Hospital and University of British Columbia, 4480 Oak Street, Vancouver, BC V6H 3 V4, Canada

Keywords Brain tumor · Cerebellar astrocytoma · Neurosurgery · Pediatric · Outcome · Treatment

Introduction

Pediatric cerebellar astrocytomas (CAs) are one of the most common pediatric tumors and the most common central nervous system tumor in childhood. Almost all of these tumors are low grade, and malignant transformation is rare. Complete surgical resection of the tumor is generally the goal and is achievable in most cases. Although largely considered a surgical disease, recurrent or progressive tumors with extension into the cerebellar peduncles or brainstem can be treated with adjunctive therapies such as radiation therapy and chemotherapy. It has been known to be a tumor with good long-term results after surgery since 1931 [17]. However, even without a gross total resection (GTR), the prognosis is very favorable with stabilization and even regression seen. New research, focusing on molecular and cell biology, has the potential for predicting outcomes and creating novel therapies. This paper reviews the epidemiology, presentation, diagnosis, pathology, microbiology, management, and future directions in regards to pediatric CA.

Epidemiology

Low-grade gliomas are the most common central nervous system (CNS) tumors in childhood. Of these, benign CAs are the most prevalent, accounting for 15–25 % of all pediatric CNS tumors [28] and 25–35 % of childhood posterior fossa tumors [14]. Most CAs are diagnosed in children less than 10 years old, with peak incidence between 6 and 8 years of age. The sex distribution is fairly equal, with some series

showing a slight male predominance [1]. Rare cases of disseminated disease or more aggressive cerebellar pilomyxoid-spectrum astrocytomas have been reported [23]. Higher-grade anaplastic astrocytomas and glioblastomas are rare in the pediatric population, and if seen, tend to occur in the second decade of life.

Pathology

On gross appearance, the typical CA has a cyst with a solid component in the wall (mural nodule). The cyst contains xanthachromic fluid, and, apart from the mural nodule, the cyst wall may have tumor in it or may consist mainly of non-neoplastic gliotic tissue. The solid tumor component of the tumor is rubbery and pink-gray in color (Fig. 1). Other CAs are solid, and some are primarily cystic, with no distinct mural nodule.

By far, the most common CA type is pilocytic astrocytoma (PA) in over 75 % of cases [65]. This benign tumor is classified as World Health Organization (WHO) Grade I [46] and has alternating areas of loosely knit tissue and compact elongated and fibrillated cells. Rosenthal fibers are also apparent. Hypercellularity, biphasic patterns, eosinophilic granular bodies, pleomorphism, endothelial proliferation, and mitoses can be present but do not usually impact prognosis [40]. MIB proliferation index (PI) was found to not affect outcomes [34, 63], even though a significant difference was discovered between PAs with cysts (3.7 %) and those that were predominantly solid tumors (6.9 %) [63]. Infiltration of the adjacent brain can be seen, to varying degrees, in classic PA as well. It has been reported in one study that a combination of certain morphologic features found in the tumor is associated with a poor outcome: lack of degenerative-type nuclear atypia, presence of >25 % oligodendroglial morphology, and presence of leptomeningeal invasion [34]. However, this has not been identified in other studies.

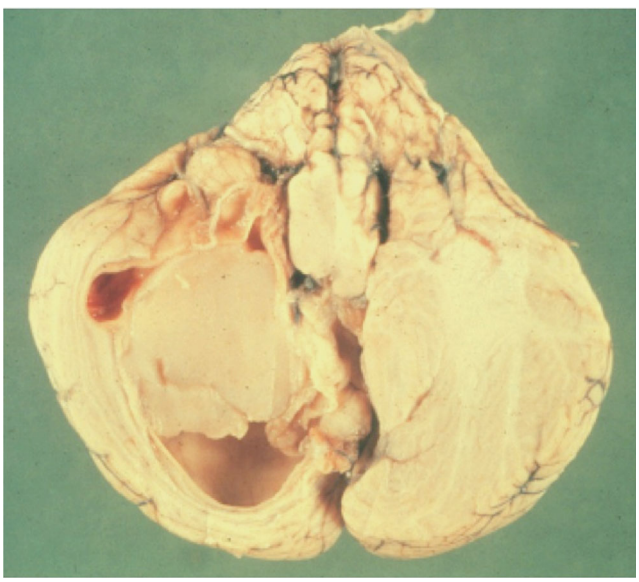

Fig. 1 Gross specimen of a classic cerebellar astrocytoma with a cystic component and solid mural nodule

Other rare types of PA have been reported in the literature. Similar to classic PA, those PAs with a diffuse pattern of growth ("diffuse variant") appear to harbor the *BRAF-RAF* fusion and have good long-term outcomes as well [38]. In addition, a large series of over 2200 PA (adult and children) recognized 1.7 % of tumors to have anaplastic features and more aggressive behavior [62].

Distinct from PA, including the diffuse variant of PA, diffuse astrocytomas (DA) are classified as WHO Grade II [46]. This type has indistinct borders with more compact and atypical cells. For pediatric cerebellar tumors, it is debated whether this histologic subtype has any impact on prognosis [7, 15].

Molecular and cell biology

Tumorgenesis of CA is not well understood. Genetic alterations seen in high-grade gliomas such as TP53 mutation, MGMT methylation, EGFR amplification, and PTEN loss are not found in PA [5, 34, 35, 54, 60]. No consistent pattern of loss of heterozygosity (LOH) on 1p or 19q has been identified, and none have shown an association with outcome. However, one study did identify cerebellar PAs with LOH on 17p13 to have worse outcomes in their cohort [35].

Despite this, several studies have identified an aberration in chromosome 7, the vast majority being a tandem duplication at 7q34 resulting in a *KIAA1549:BRAF* fusion gene in the majority of cases. A smaller number of tumors have a *BRAF* point mutation or alternative *BRAF-RAF* fusions. All cause alterations in the MEK/mitogen-activated protein kinase (MAPK) pathway and increased transcriptional activity and cellular proliferation [26, 42, 57, 67]. Because of this, PA is considered predominantly a single pathway disease [43]. However, outcomes do not appear to be affected by the absence or presence of this alteration.

More recent studies have reported other genetic abnormalities in CA. Copy number alterations 2p11.2 amp and 9p11.2 amp were correlated with better prognosis, whereas 1p36.21 was associated with worse outcome [5]. Lambert et al. investigated the methylation patterns of brain developmental genes in PA. In this study, differential methylation was important to the development of PA arising at different locations in the brain. Furthermore, global levels of gene hypomethylation, including SIX3, NR2E1, EN2, IRX2, and PAX3, were seen in infratentorial compared to supratentorial PA [50]. Finally, profiling has also revealed 13 underexpressed and 20 overexpressed tumor microRNAs. Increased expression of

protein targets such as BBX3, METAP2, and NFIB was reported as well [33].

Other mechanisms under investigation include angiogenesis, tumor microenvironment, telomere maintenance, and glioma-associated antigens [68].

Clinical presentation

Pediatric CA are slow growing tumors that produce symptoms based on their posterior fossa location and the sequelae of increased intracranial pressure (ICP) secondary to hydrocephalus. Symptoms are generally long standing, and nearly half the patients have symptoms for longer than 6 months at the time of diagnosis [25].

Headache is the most common presenting symptom and is seen in over 90 % of cases [1, 19, 20, 65]. This headache tends to worsen with exertion and during periods of recumbence. Often, the child's headache will be at its worst during or just after sleep. The major reason for the headache is from increased ICP, caused by obstruction of cerebral spinal fluid (CSF) circulation at the level of the aqueduct of Sylvius or 4th ventricle, as hydrocephalus has been seen on imaging in over 90 % of all cases [22, 56]. Vomiting and lethargy are also common presenting features, worsening as the hydrocephalus increases in severity and duration. Papilledema is frequently seen. Physical examination findings related to increased ICP may include 6th cranial nerve palsy, upgaze restriction, and increased head circumference are seen less frequently [56]. In a few cases, the presentation can be the acute onset of drowsiness or coma, which necessitates emergency management.

The cerebellar location of the tumor often results in posterior fossa localizing symptoms such as ataxia, horizontal nystagmus, and dysmetria. Ataxia may be difficult to notice in children and may manifest as a regression in walking. In younger children, ataxia may just be seen as clumsiness during learning the ability to walk. Occasionally, neck stiffness or torticollis may be the only presenting tumor of a posterior fossa tumor, especially if the tumor extends caudally out of the 4th ventricle. However, this is more typical of an ependymoma.

Diagnosis

Due to the slow growing nature of CAs and the ability of the pediatric brain to compensate, many tumors are very large at the time of diagnosis. Computed tomographic (CT) scans illustrate the presence of a mass, and the extent of hydrocephalus and magnetic resonance imaging (MRI) gives further detail regarding the relationship to surrounding brain structures. Although spread is uncommon, an MRI of the spine is often done concurrently to rule out metastatic deposits.

The classical appearance of the pilocytic astrocytoma (PA) is a cystic mass, with an eccentric solid component, typically occurring in the cerebellar astrocytoma. On CT scan, the solid component is usually hypodense. On MRI, the lesions appear hypointense on T1 sequence and hyperintense on T2 sequence, with avid contrast enhancement in the solid component of the tumor. On diffusion scan, there is no restriction of diffusion and usually increased diffusivity relative to the normal adjacent brain (Fig. 2). The cyst wall may comprise only gliotic cerebellar tissue, in which case there is no contrast enhancement or a thin, smooth rim of enhancement only (Fig. 3a). However, sometimes there is tumor in the cyst wall, in which case there is usually irregular and thicker enhancement in the cyst wall on CT or MRI scans (Fig. 3b). Diffuse astrocytomas (DAs) have variable enhancement and less defined borders on imaging. Other CAs are cystic, without a noticeable mural nodule (Fig. 4), while some are mainly solid (Fig. 5). The vast majority (90 %) of these solid tumors are midline and are therefore more difficult to distinguish radiographically from medulloblastomas or ependymomas. The hypodensity of the solid tumor on CT scan and the lack of restricted diffusion (with increased diffusivity) and lack of ionositol peak on MRI in CA can help distinguish it from the ependymoma and medulloblastoma [47]. Involvement of the brain stem radiographically is seen in a minority of cases of CA [39].

Management and outcomes

First-line treatment for CA is surgical resection, with a goal of GTR if possible without causing unacceptable neurologic deficits. In cystic lesions, without tumor in the cyst wall, only the solid component requires removal [12]. As mentioned above, the pattern of enhancement on the MRI scans may be helpful in predicting if tumor is or is not present in the cyst wall. Regardless of the suggestive findings on the MRI, whether or not there is tumor in the cyst wall is usually obvious at the time of surgery, based on a smooth, white, glistening cyst wall in the absence of tumor. Ultimately, it is the surgical findings that are relied on in deciding if the cyst wall contains tumor and should be removed. Reported rates of GTR range from 50 to 89 % [53, 56, 70]. The usually reported barrier to GTR is involvement of the brainstem and cerebellar peduncles, but in the series reported by Steinbok et al. in half of the patients where GTR was not achieved, residual tumor was elsewhere. In that series, some tumor resections were incomplete because of the concern of the surgeons that further resection might result in neurological deficits. Indeed, with this less aggressive surgical approach than the same surgeons had used previously, an acceptable GTR rate was achieved with a reduction in the incidence of permanent neurologic deficits caused by the surgery [70].

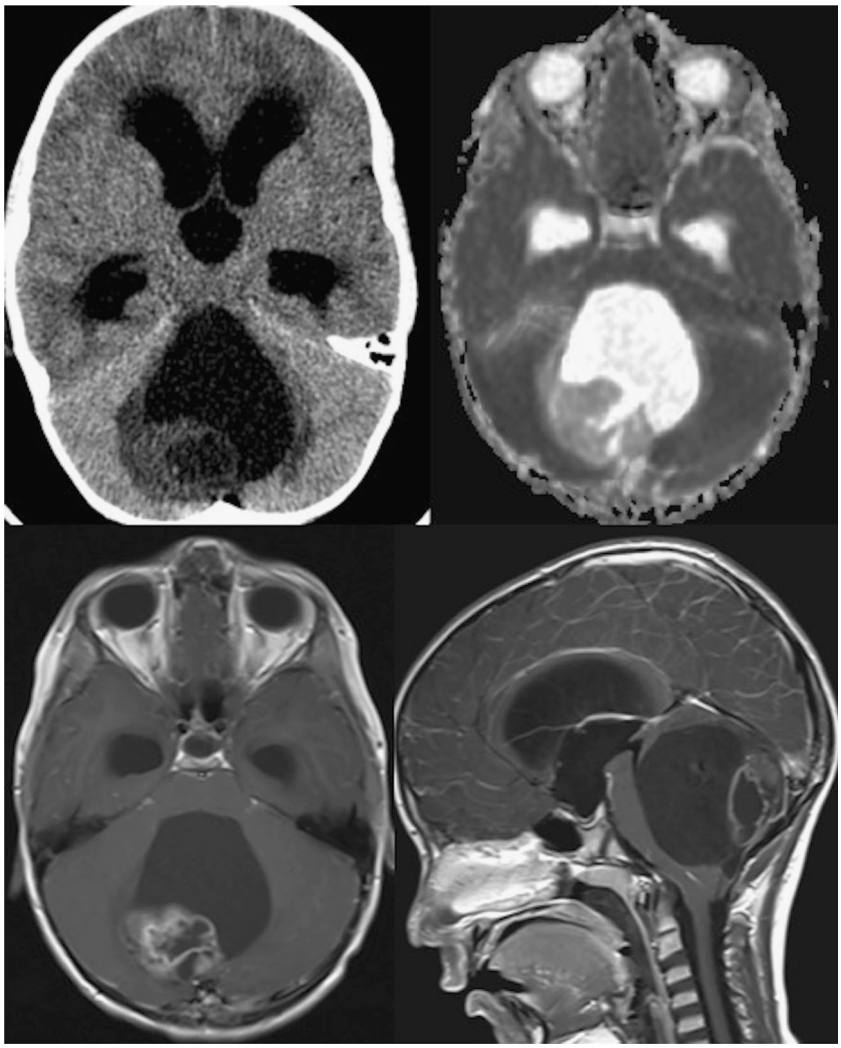

Fig. 2 Classical appearance of a pilocytic astrocytoma with a hypodense nodule on CT and increased diffusivity and solid contrast enhancement on MRI

Children with GTR, documented on postoperative MRI, need no further treatment and have an overall 10-year survival rate of over 90 % with only rare tumor recurrences [68]. However, complete resection has been found to be the most important prognostic factor in progression-free survival (PFS) of low-grade CA [72, 73].

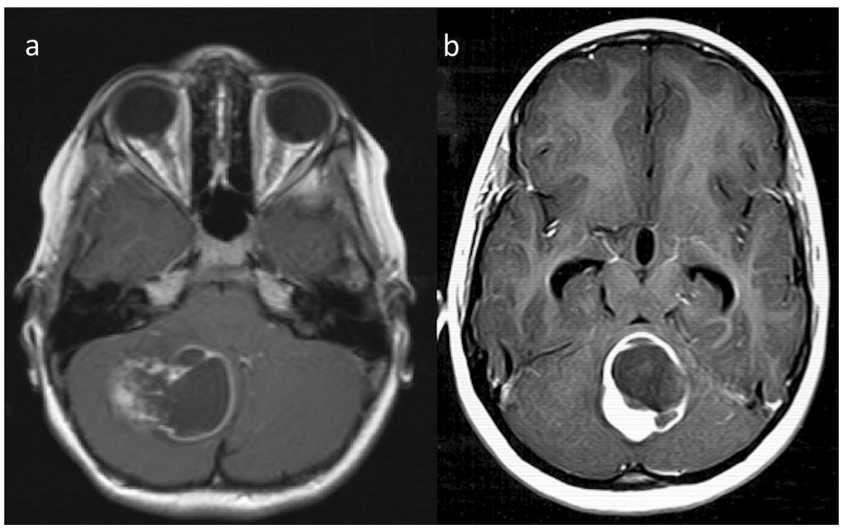

Fig. 3 Cerebellar astrocytoma illustrating a gliotic cyst wall without tumor (**a**) and an enhancing cyst wall with tumor (**b**) on MRI with contrast

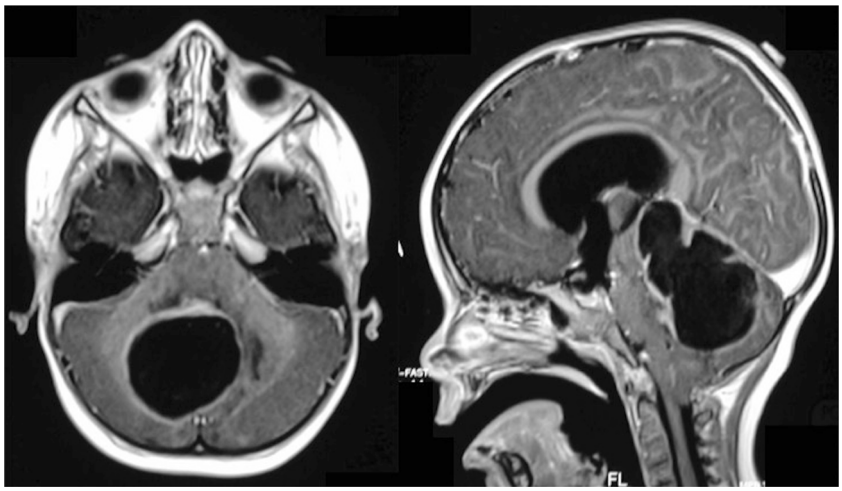

Fig. 4 Cystic appearance of a cerebellar astrocytoma without a noticeable mural nodule on MRI with contrast

Overall mortality is very low with rates from 0 to 4 % in large series [22, 53, 56].

Subtotal resection may occur, because the surgeon intentionally left tumor behind to avoid morbidity to the patient, but may also occur unintentionally. For example, the surgeon may think that a complete resection has been achieved, but on the postoperative imaging done typically within 72 h, tumor residual may be seen. When such unexpected residual tumor is identified and the tumor residual can be resected safely, immediate reoperation to remove this tumor is recommended. For those patients, in whom there is residual tumor that is not deemed to be safe to resect totally, treatment is more controversial. Because of the indolent nature of CA, the decision for further treatment is usually deferred until there is progression on imaging or clinical symptoms. Studies have reported 5-year PFS of 45–65 % for residual tumor of any size and long-term stability or regression of residual tumor in 33–65 % [24, 53, 66, 68, 69]. The mechanism of spontaneous tumor regression is unknown. Hypotheses include ischemia secondary to interference to the tumor blood supply during initial resection, inhibition of angiogenesis, or an apoptotic mechanism [69]. Therefore, a "wait and see" approach could be recommended until residual tumor growth or new tumor recurrence is confirmed [6, 53].

The management of recurrent or progressive tumor is surgical, with the goal of achieving a gross total resection. Often, this is possible, even when the initial resection has been incomplete [10, 22]. For the rare tumors that are inaccessible surgically or for tumors that have recurred after more than one resection, other treatments, such as radiotherapy and chemotherapy, may be considered.

Chemotherapy has become the initial adjuvant therapy if resection is not feasible. Regimens of carboplatin and vincristine have been effective, but up to 42 % of children experience hypersensitivity reactions [49, 74]. Alternatively, combination 6-thioguanine, procarbazine, CCNU, vincristine with or without dibromodulcitol or vinblastine monotherapy has also had positive outcomes [4, 59].

Adjunctive radiotherapy is generally avoided in the management of low-grade cerebellar astrocytomas (especially in young children) due to adverse neurocognitive effects. Whereas some studies report increased PFS [29, 58], others

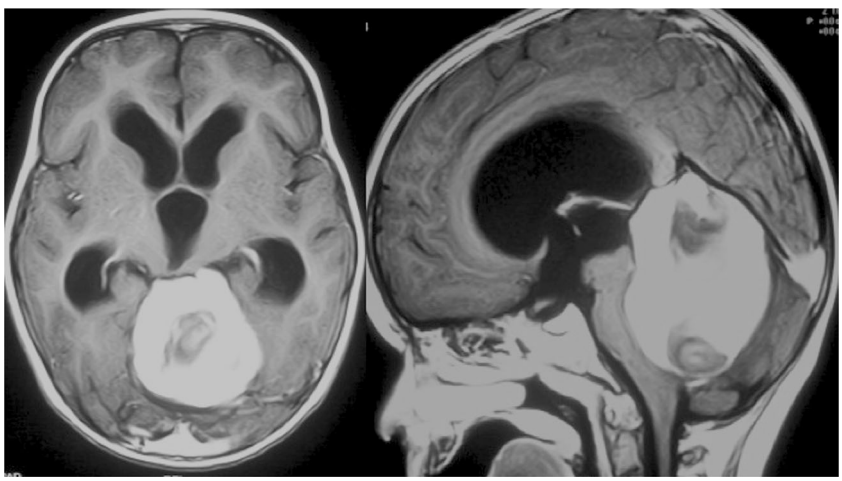

Fig. 5 Midline solid appearance of a cerebellar astrocytoma on MRI with contrast

show no evidence of increased overall survival [24, 58]. Furthermore, malignant transformation and radiation-induced side effects have been observed [1]. More recent reports have suggested that conformal proton radiotherapy [36] and stereotactic radiosurgery [32] may provide a safe and effective treatment strategy for progressive and inaccessible tumors and these modalities warrant further investigation.

As mentioned previously, hydrocephalus is exceedingly common in patients with CA and requires consideration of treatment before, during, and after tumor resection. In the acute setting, if the tumor has a large cystic component, it may be possible to drain the cyst and perform surgery at a later time. Other techniques used to treat hydrocephalus prior to tumor removal involve the placement of an external ventricular drain (EVD), insertion of a ventriculoperitoneal shunt, or a completion of a third ventriculostomy [22]. In at least one institution, an EVD is placed in every patient for intraoperative CSF drainage [53]. Other centers are more selective. Persistent hydrocephalus necessitated shunting is as high as 15 % in one large series [22].

Postoperative surveillance

Postoperative MRI surveillance is somewhat controversial, particularly when GTR has been achieved, as the risk of recurrence after GTR is very low. Furthermore, many pediatric patients require a general anesthetic for an MRI. This carries with it a small, but significant risk of 1–5 % for adverse effects of hypoxemia, central apnea, and airway obstruction [16, 52]. In addition, resource utilization and cost must be considered. Another consideration is that there tends to be additional anxiety for the child and parents as the time for a surveillance scan approaches and this can be alleviated by doing fewer surveillance scans.

Some studies have suggested that routine MRI surveillance in patients with GTR is unnecessary [71]. Conversely, others have reported recurrence of tumor, even with GTR, up to 10 years after the initial resection and recommend 10 years as a reasonable follow-up period for neuroimaging studies [22, 53]. There is no consensus on a surveillance schedule after GTR, but most centers obtain a postoperative MRI at 3–6 months, annually for 5 years and then decreasing in frequency, perhaps every 5 years thereafter. For those patients with residual tumor after resection, a similar schedule for the first 5 years may be reasonable if there is no progression, but more frequent long-term routine surveillance is recommended, unless the tumor regresses completely.

Functional outcome

With the excellent overall survival of children with CA, the long-term functional outcomes and QOL are important issues. These outcomes may be impacted by the tumor itself, the preoperative duration of symptoms, ventricular dilation, the surgical resection and its complications, and the morbidity of any adjuvant treatments. Outcomes are generally excellent, with the vast majority of patients with normal functionality and educational levels [70]. Due-Tonnessen et al. found a normal Barthel index (for activities of daily living) in 97 % of their patients [22]. Likewise, quality of life (QOL) indicators have been shown to be similar to the general population [48, 75], even though some patients have permanent neurologic deficits and emotional disorders [3, 18]. Permanent neurologic deficits have been reported ranging from 15 % to greater than 50 % [3, 70, 75]. Cerebellar mutism can be seen, especially in large, midline, solid tumors with rates ranging from 0 to 8 % [22, 53, 70]. Overall, most of these sequelae result in mild cerebellar dysfunction, which include motor slowness, writing difficulties, fine manual skill defects, balance, and speech difficulties. Cognitive deficits are observed less frequently, and over 80 % of patients participated in normal schooling [3, 70].

Future directions

Although surgical resection remains the mainstay of treatment for CAs, molecular and biologic therapies based on the discoveries discussed above are being investigated. These therapies are largely being developed for deeper-located, noncerebellar tumors but can also be applied to recurrent and incompletely resected CAs. Deregulated BRAF activity in the MEK/MAPK pathway activates mTOR, a common signaling molecule in neurofibromatosis 1 (NF1) astrocytomas as well. This finding suggests that mTOR may be a target for both treatment of sporadic and NF1 PAs with the use of rapamycin analogs [13, 45]. These analogs are currently being used in treating subependymal giant cell astrocytomas in tuberous sclerosis syndrome [27]. Other studies involving small molecule MEK inhibitors have shown encouraging results in other neoplasms [2, 8, 11, 51, 61]. BRAF and growth factor receptors are also being a target for inhibition [21, 41, 45, 64].

Second-line chemotherapy options are also being explored. Weekly vinblastine [9], temozolomide [30, 44], bevacuzimab [37] and combination bevacuzimab and irinotecan [31, 55], have all been used in promising studies of other low-grade astrocytomas. As more is learned about the molecular biology of CA, targeted drugs may emerge as useful therapeutic options.

Conclusion

Pediatric cerebellar astrocytomas are benign tumors with very good long-term survival rates and functional outcomes.

Complete surgical resection is the first-line treatment with repeat resection utilized in cases of recurrent or progressive surgically accessible tumors. The natural history of incompletely resected CA is variable, with spontaneous regression or stabilization in a significant percentage. Hence, radiotherapy or chemotherapy should be reserved for cases with surgically inaccessible, progressive lesions.

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval For this type of study, formal consent is not required.

References

1. Abdollahzadeh M, Hoffman HJ, Blazer SI, Becker LE, Humphreys RP, Drake JM, Rutka JT (1994) Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980–1992. Childs Nerv Syst 10:380–383
2. Adjei AA, Cohen RB, Franklin W, Morris C, Wilson D, Molina JR, Hanson LJ, Gore L, Chow L, Leong S, Maloney L, Gordon G, Simmons H, Marlow A, Litwiler K, Brown S, Poch G, Kane K, Haney J, Eckhardt SG (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 26:2139–2146
3. Ait Khelifa-Gallois N, Laroussinie F, Puget S, Sainte-Rose C, Dellatolas G (2014) Long-term functional outcome of patients with cerebellar pilocytic astrocytoma surgically treated in childhood. Brain Inj 10:1–8
4. Ater J, Holmes E, Zhou T, Mazewski C, Roberts W, Vezina G, Booth T, Freyer D, Kadota R, Jakacki R, Packer R, Prados M, Pollack I (2008) Abstracts from the thirteenth international symposium on pediatric neuro-oncology: results of COG protocol A9952—a randomized phase 3 study of two chemotherapy regimens for incompletely resected low-grade glioma in young children. Neuro Oncol 10:451
5. Belirgen M, Berrak SG, Ozdag H, Bozkurt SU, Eksioglu-Demiralp E, Ozek MM (2012) Biologic tumor behavior in pilocytic astrocytomas. Childs Nerv Syst 28:375–389
6. Benesch M, Eder HG, Sovinz P, Raith J, Lackner H, Moser A, Urban C (2006) Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is re-treatment needed? A single center experience from 1983 to 2003. Pediatr Neurosurg 42:159–164
7. Bernhardtsen T, Laursen H, Bojsen-Møller M, Gjerris F (2003) Subclassification of low-grade cerebellar astrocytoma: is it clinically meaningful? Childs Nerv Syst 19:729–735
8. Blumenschein GR Jr, Gatzemeier U, Fossella F, Stewart DJ, Cupit L, Cihon F, O'Leary J, Reck M (2009) Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. J Clin Oncol 27: 4274–4280
9. Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, Hukin J, Bartels U, Foreman N, Kellie S, Hilden J, Etzl M, Wilson B, Stephens D, Tabori U, Baruchel S (2012) Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30:1358–1363
10. Bowers DC, Krause TP, Aronson LJ, Barzi A, Burger PC, Carson BS, Weingart JD, Wharam MD, Melhem ER, Cohen KJ (2012) Second surgery for recurrent pilocytic astrocytoma in children. Pediatr Neurosurg 34:229–234
11. Britten CD, Adjei AA, Millham R, Houk BE, Borzillo G, Pierce K, Wainberg ZA, LoRusso PM (2014) Phase I study of PF-04691502, a small-molecule, oral, dual inhibitor of PI3K and mTOR, in patients with advanced cancer. Invest New Drugs 32:510–517
12. Bui C, Jeelani Y, Grimm J, Yousef A, Da Silva S, McComb JG, Krieger MD (2013) Does the post-operative presence of an enhancing cyst wall in pilocytic astrocytoma indicate higher risk of tumor recurrence? Childs Nerv Syst 29:1726
13. Chen YH, Gutmann DH (2014) The molecular and cell biology of pediatric low-grade gliomas. Oncogene 33:2019–2026
14. Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR (1994) The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg 20:19–29
15. Conway PD, Oechler HW, Kun LE, Murray LE (1991) Importance of histologic condition and treatment of pediatric cerebellar astrocytoma. Cancer 67:2772–2775
16. Cravero JP, Beach ML, Blike GT, Gallagher SM, Hertzog JH (2009) The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. Anesth Analg 108:795–804
17. Cushing H (1931) Experiences with the cerebellar astrocytomas: a critical reiew of seventy-six cases. Surg Gynecol Obstet 52:129–204
18. Daszkiewicz P, Maryniak A, Roszkowski M, Barszcz S (2009) Long-term functional outcome of surgical treatment of juvenile Pilocytic astrocytoma of the cerebellum in children. Childs Nerv Syst 25:855–860
19. Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P (1998) Grading of astrocytomas. A simple and reproducible method. Cancer 62:2152–2165
20. Davis CH, Joglekar VM (1981) Cerebellar astrocytomas in children and young adults. J Neurol Neurosurg Psychiatry 44:820–828
21. Dieci MV, Arnedos M, Andre F, Soria JC (2013) Fibroblast growth factor receptor inhibitors as a cancer treatment: from a biologic rationale to medical perspectives. Cancer Discov 3:264–279
22. 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
23. El Beltagy MA, Atteya MM, El-Haddad A, Awad M, Taha H, Kamal M, El Naga SA (2014) Surgical and clinical aspects of cerebellar pilomyxoid-spectrum astrocytomas in children. Childs Nerv Syst 30:1045–1053
24. Fisher BJ, Leighton CC, Vujovic O, Macdonald DR, Stitt L (2001) Results of a policy of surveillance alone after surgical management of pediatric low grade gliomas. Int J Radiat Oncol Biol Phys 51: 704–710
25. Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD, Repka MX, Cohen KJ, Burger PC (2008) Outcome analysis of childhood low-grade astrocytomas. Pediatr Blood Cancer 51:245–250
26. Forshew T, Tatevossian RG, Lawson AR, Ma J, Neale G, Ogunkolade BW, Jones TA, Aarum J, Dalton J, Bailey S, Chaplin T, Carter RL, Gajjar A, Broniscer A, Young BD, Ellison DW, Sheer D (2009) Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. J Pathol 218: 172–181

27. Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, Dinopoulos A, Thomas G, Crone KR (2006) Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 59:490–498
28. Freeman CR, Farmer JP, Montes J (1998) Low-grade astrocytomas in children: evolving management strategies. Int J Radiat Oncol Biol Phys 41:979–987
29. Garcia DM, Marks JE, Latifi HR, Kliefoth AB (1990) Childhood cerebellar astrocytomas: is there a role for postoperative irradiation? Int J Radiat Oncol Biol Phy 18:815–818
30. Gururangan S, Fisher MJ, Allen JC, Herndon JE 2nd, Quinn JA, Reardon DA, Vredenburgh JJ, Desjardins A, Phillips PC, Watral MA, Krauser JM, Friedman AH, Friedman HS (2007) Temozolomide in children with progressive low-grade glioma. Neuro Oncol 9:161–168
31. Gururangan S, Fangusaro J, Poussaint TY, McLendon RE, Onar-Thomas A, Wu S, Packer RJ, Banerjee A, Gilbertson RJ, Fahey F, Vajapeyam S, Jakacki R, Gajjar A, Goldman S, Pollack IF, Friedman HS, Boyett JM, Fouladi M, Kun LE (2014) Efficacy of Bevacizumab plus irinotecan in children with recurrent low-grade gliomas–a pediatric brain tumor consortium study. Neuro Oncol 16: 310–317
32. Hadjipanayis CG, Kondziolka D, Gardner P, Niranjan A, Dagam S, Flickinger JC, Lunsford LD (2002) Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary. J Neurosurg 97:56–64
33. Ho CY, Bar E, Giannini C, Marchionni L, Karajannis MA, Zagzag D, Gutmann DH, Eberhart CG, Rodriguez FJ (2013) MicroRNA profiling in pediatric pilocytic astrocytoma reveals biologically relevant targets, including PBX3, NFIB, and METAP2. Neuro Oncol 15:69–82
34. 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
35. Horbinski C, Hamilton RL, Nikiforov Y, Pollack IF (2010) Association of molecular alterations, including BRAF, with biology and outcome in pilocytic astrocytomas. Acta Neuropathol 119: 641–649
36. Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredo LN, Grove RI, Slater JD (2002) Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlenther Onkol 178:10–17
37. Hwang EI, Jakacki RI, Fisher MJ, Kilburn LB, Horn M, Vezina G, Rood BR, Packer RJ (2013) Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer 60:776–782
38. Ida CM, Lambert SR, Rodriguez FJ, Voss JS, Mc Cann BE, Seys AR, Halling KC, Collins VP, Giannini C (2012) BRAF alterations are frequent in cerebellar low-grade astrocytomas with diffuse growth pattern. J Neuropathol Exp Neurol 71:631–639
39. Ilgren EB, Stiller CA (1987) Cerebellar astrocytomas. Part I Macroscopic and microscopic features. Clin Neuropathol 6: 185–200
40. Ilgren EB, Stiller CA (1987) Cerebellar astrocytomas. Part II Pathologic features indicative of malignancy. Clin Neuropathol 6: 201–214
41. Iyer R, Varela CR, Minturn JE, Ho R, Simpson AM, Light JE, Evans AE, Zhao H, Thress K, Brown JL, Brodeur GM (2012) AZ64 inhibits TrkB and enhances the efficacy of chemotherapy and local radiation in neuroblastoma xenografts. Cancer Chemother Pharmacol 70:477–486
42. Jones DT, Kocialkowski S, Liu L, Pearson DM, Bäcklund LM, Ichimura K, Collins VP (2008) Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68:8673–8677
43. Jones DT, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz HJ, Zichner T, Lambert SR, Ryzhova M, Quang DA, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho YJ, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo ML, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, International Cancer Genome Consortium PedBrain Tumor Project (2013) Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45:927–932
44. Khaw SL, Coleman LT, Downie PA, Heath JA, Ashley DM (2007) Temozolomide in pediatric low-grade glioma. Pediatr Blood Cancer 49:808–811
45. Kilday JP, Bartels UK, Bouffet E (2014) Targeted therapy in pediatric low-grade glioma. Curr Neurol Neurosci Rep 14:441
46. Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. Brain Pathol 3:255–268
47. Koral K, Alford R, Choudhury N, Mossa-Basha M, Gargan L, Gimi B, Gao A, Zhang S, Bowers DC, Koral KM, Izbudak I (2014) Applicability of apparent diffusion coefficient ratios in preoperative diagnosis of common pediatric cerebellar tumors across two institutions. Neuroradiology 56:781–788
48. 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
49. Lafay-Cousin L, Sung L, Carrett AS, Hukin K, Wilson B, Johnston DL, Zelcer S, Silva M, Odame I, Mpofu C, Strother D, Bouffett E (2008) Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium. Cancer 112:892–899
50. Lambert SR, Witt H, Hovestadt V, Zucknick M, Kool M, Pearson DM, Korshunov A, Ryzhova M, Ichimura K, Jabado N, Fontebasso AM, Lichter P, Pfister SM, Collins VP, Jones DT (2013) Differential expression and methylation of brain developmental genes define location-specific subsets of pilocytic astrocytoma. Acta Neuropathol 126:291–301
51. Lorusso PM, Adjei AA, Varterasian M, Gadgeel S, Reid J, Mitchell DY, Hanson L, DeLuca P, Bruzek L, Piens J, Asbury P, Van Becelaere K, Herrera R, Sebolt-Leopold J, Meyer MB (2005) Phase I and pharmacodynamic study of the oral MEK inhibitor CI-1040 in patients with advanced malignancies. J Clin Oncol 23: 5281–5293
52. Machata AM, Willschke H, Kabon B, Kettner SC, Marhofer P (2008) Propofol-based sedation regimen for infants and children undergoing ambulatory magnetic resonance imaging. Br J Anaesth 101:239–243
53. Ogiwara H, Bowman RM, Tomita T (2012) Long-term follow-up of pediatric benign cerebellar astrocytomas. Neurosurgery 70:40–47
54. Ohgaki H, Eibl RH, Schwab M, Reichel MB, Mariani L, Gehring M, Petersen I, Höll T, Wiestler OD, Kleihues P (1993) Mutations of the p53 tumor suppressor gene in neoplasms of the human nervous system. Mol Carcinog 8:74–80
55. Packer RJ, Jakacki R, Horn M, Rood B, Vezina G, MacDonald T, Fisher MJ, Cohen B (2009) Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan. Pediatr Blood Cancer 52:791–795
56. Pencalet P, Maixner W, Sainte-Rose C, Lellouch-Tubiana A, Cinalli G, Zerah M, Pierre-Kahn A, Hoppe-Hirsch E, Bourgeois M, Renier

D (1999) Benign cerebellar astrocytomas in children. J Neurosurg 90:265–273
57. Pfister S, Janzarik WG, Remke M, Ernst A, Werft W, Becker N, Toedt G, Wittmann A, Kratz C, Olbrich H, Ahmadi R, Thieme B, Joos S, Radlwimmer B, Kulozik A, Pietsch T, Herold-Mende C, Gnekow A, Reifenberger G, Korshunov A, Scheurlen W, Omran H, Lichter P (2008) BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest 118:1739–1749
58. Pollack IF, Claassen D, Al-Shboul Q, Janosky JE, Deutsch M (1995) Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. J Neurosurg 82:536–554
59. 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 32:235–241
60. 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 54:1324–1330
61. Rinehart J, Adjei AA, Lorusso PM, Waterhouse D, Hecht JR, Natale RB, Hamid O, Varterasian M, Asbury P, Kaldjian EP, Gulyas S, Mitchell DY, Herrera R, Sebolt-Leopold JS, Meyer MB (2004) Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. J Clin Oncol 22:4456–4462
62. Rodriguez FJ, Scheithauer BW, Burger PC, Jenkins S, Giannini C (2010) Anaplasia in pilocytic astrocytoma predicts aggressive behavior. Am J Surg Pathol 34:147–160
63. Roessler K, Bertalanffy A, Jezan H, Ba-Ssalamah A, Slavc I, Czech T, Budka H (2002) Proliferative activity as measured by MIB-1 labeling index and long-term outcome of cerebellar juvenile pilocytic astrocytomas. J Neurooncol 58:141–146
64. Rusconi P, Caiola E, Broggini M (2012) RAS/RAF/MEK inhibitors in oncology. Curr Med Chem 19:1164–1176
65. Sgouros S, Fineron PW, Hockley AD (1995) Cerebellar astrocytoma of childhood: long-term follow-up. Childs Nerv Syst 11:89–96
66. Shaw EG, Wisoff JH (2003) Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro Oncol 5:153–160
67. Sievert AJ, Jackson EM, Gai X, Hakonarson H, Judkins AR, Resnick AC, Sutton LN, Storm PB, Shaikh TH, Biegel JA (2009) Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single-nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. Brain Pathol 19:449–458
68. Sievert AJ, Fisher MJ (2009) Pediatric low-grade gliomas. J Child Neurol 24:1397–1408
69. Steinbok P, Poskitt K, Hendson G (2006) Spontaneous regression of cerebellar astrocytoma after subtotal resection. Childs Nerv Syst 22:572–576
70. Steinbok P, Mangat JS, Kerr JM, Sargent M, Suryaningtyas W, Singhal A, Cochrane D (2013) Neurological morbitidy of surgical resection of pediatric cerebellar astrocytomas. Childs Nerv Syst 29: 1269–1275
71. 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
72. Villarejo F, de Diego JM, de la Riva AG (2008) Prognosis of cerebellar astrocytomas in children. Childs Nerv Syst 24:203–210
73. Wisoff JH, Sanford RA, Heier LA, Sposto R, Burger PC, Yates AJ, Holmes EJ, Kun LE (2011) Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68:1548–1554
74. Yu DY, Dahl GV, Shames RS, Fisher PG (2001) Weekly dosing of carboplatin increases risk of allergy in children. J Pediatr Hematol Oncol 23:349–352
75. 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