Primary Pediatric Brain Tumors of the Posterior Fossa: Part I

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Abstract In pediatric neuro-oncology practice, cerebellar tumors are often referred to as infratentorial tumors or tumors of the posterior fossa (a differential diagnosis is provided in Table 1). This anatomic region also contains the pons and medulla, which along with the midbrain comprise the brainstem. In Part I of this comprehensive review, three important pediatric brain tumors usually localized to the cerebellum are discussed (and summarized in Table 2): atypical teratoid/rhabdoid tumors (ATRTs), pilocytic astrocytomas, and ependymomas. In the compan-

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ion chapter (Part II), an integrated clinical and molecular overview of medulloblastoma follows. These tumors have been selected, in part, due to their clinical significance as well as recent advances in their molecular genetics and pathological classification. For these entities and others, the histopathologic, cytogenetic, and molecular factors have been integrated into the updated fourth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (Louis et al., WHO classification of tumours of the central nervous system, Revised 4th edn. IARC, Lyon, 2016a; Louis et al., Acta Neuropathol 131:803–820, 2016b).

Keywords Childhood brain tumors • Medulloblastoma • Atypical teratoid/rhabdoid tumor • ATRT • Pilocytic astrocytoma • Ependymoma • Posterior fossa • Cerebellum

Introduction

Posterior fossa tumors are located in the infratentorial space that is separated from the supratentorial space by a meningeal fold, the cerebellar tentorium. Important neuroanatomical structures located within the infratentorial space are the cerebellum with the fourth ventricle and caudal part of the brainstem that includes the pons and medulla oblongata. The posterior fossa is the site of a variety of rare primary pediatric brain tumors, including tumors from brainstem glioma, meningioma and schwannoma, hemangioblastoma, hemangiopericytoma, choroid plexus papilloma, and epidermoid cyst (Table 1; [77]). The three most common posterior fossa primary pediatric brain tumors are pilocytic astrocytoma (PA), ependymoma, and medulloblastoma (MB), all of which have associations with the cerebellum. While this chapter (Part I) will discuss pilocytic astrocytoma, ependymoma, and atypical teratoid/rhabdoid tumors (ATRTs), the following chapter (Part II) will focus primarily on MB. All of these tumors share three basic clinical and molecular characteristics (Table 2): (i) Clinical symptoms are caused by posterior fossa compression and occluding hydrocephalus and result in increased intracranial pressure with headaches, progressive nausea, vomiting, lethargy, and drowsiness. Cerebellar tumor location frequently causes ataxia. While these general symptoms do little to differentiate between posterior fossa tumors, children with ependymoma obstructing the foramen of Magendie show distinct torticollis which is rarely observed with other posterior fossa tumors, like MB or PA. (ii) Surgical tumor excision is the initial treatment of choice and, in cases where complete surgical removal is impossible, is combined with targeted radiotherapy, chemotherapy, or both depending on the tumor histology and age of the child. (iii) An emerging common molecular theme is that tumors located at different neuroanatomical locations have distinct cytogenetic/gene expression signatures. This has important implications for the selection of future molecular targets and new therapeutic intervention strategies.

Table 1 Posterior fossa mass: differential diagnosis

Pilocytic astrocytoma
Medulloblastoma
Ependymoma
Atypical teratoid/rhabdoid tumor (ATRT)
Brainstem glioma
Metastatic deposits
Hemangioblastoma
Teratoma
Dermoid cyst
Meningioma
Vestibular schwannoma
Lymphoma
Ganglioglioma
Lhermitte-Duclos disease

Atypical Teratoid/Rhabdoid Tumor (ATRT)

Epidemiology

Atypical teratoid/rhabdoid tumors (ATRTs) are highly aggressive embryonal tumors that predominantly affect very young children. Until recently, this tumor type was thought to be universally fatal [99, 34]. These brain tumors have historically been characterized by their aggressive behavior and poor prognosis, with a median survival ranging from 6 to 11 months [13, 51, 69, 92]. ATRTs are the most common malignant CNS tumor affecting children younger than 6 months of age [22]. Approximately 70% of cases arise in children younger than 1 year of age, and 90% occur before 3 years of age [38], with a median age of 18 months [24].

Overall, ATRTs are estimated to comprise 1–3% of pediatric brain tumors [53, 58], but they account for 20% of CNS tumors in children under the age of 3 years [53]. The CBTRUS data from 2008 to 2012 determined the incidence of ATRT to be 0.34 per 100,000 population in children aged 0–4 years and 0.02 per 100,000 population in children aged 5–9 years [68]. Relative survival estimates for embryonal tumors are low but vary significantly by histology. The current 10-year survival rate for ATRT is 26.5% [68].

SEER data between 1973 and 2010 identified 174 cases of ATRT. There was a significantly higher incidence in males (56.3%), Caucasians (59.1%), and children less than 3 years (80.5%). The most common primary sites were the cerebellum (17.8%), the ventricles (16.1%), and the frontal lobe (12.6%) [53]. In the past,

Table 2 Posterior fossa tumors

	Medulloblastoma	Ependymoma	ATRT	Pilocytic astrocytoma
Age group	Peak incidence 5–9 years	Mean age 6 years	Peak incidence <3 years, median age at diagnosis 18 months	Peak incidence 5–15 years
Gender	M>F (1.6–1)	M=F	M>F (1.5:1)	M=F
Molecular genetics	WNT, sonic hedgehog (SHH), group 3, and group 4	PF-A: epigenetic aberration PF-B: chromosomal aberration	Mutation or inactivation of INI1/hSNF5/BAF47, 90% of tumors have loss of INI1 nuclear staining, indicative of biallelic inactivation of SMARCB1b	>70% of cerebellar PA have *BRAF-KIAA* fusion gene, germline mutations in *NF1* with optic pathway PA
Histopathology	Classic MB, desmoplastic MB, large cell MB, anaplastic MB, and MB with extensive nodularity (MBEN)	WHO grade I–IV, myxopapillary, subependymoma, ependymoma and anaplastic ependymoma	Characterized by rhabdoid cells, small round blue cell tumors	WHO grade I rarely show anaplasia
Management	Maximal safe surgical resection, craniospinal radiation (for those >3 years), and adjuvant chemotherapy	Surgical resection with adjuvant radiotherapy, chemotherapy in young children or patients with residual/recurrent disease	Surgical resection followed by intensive chemotherapy and focal or craniospinal radiation, high-dose chemotherapy with stem cell rescue is also an option	Surgical resection, radiation therapy for progressive disease
Prognosis	10-year survival is 63.3%; 5-year overall survival based on subgroups: WNT (>90%), SHH (~75%), group 3 (40–60%), and group 4 (~75%)	5-year overall survival rate 23–69%	Poor survival, though improving, with median survival of 10–11 months	10-year overall survival rate >90%

ATRT was associated with an extremely poor prognosis, with mean overall survival ranging from 6 to 18 months [69, 96]. SEER data showed a mean overall survival of 3.2 ± 0.4 years, while overall and cancer-specific mortality were 63.2% and 56.3%, respectively. Most ATRT cases were treated with surgery alone (58.0%), followed by a combination of surgery and radiation (34.3%), no treatment (6.5%), and radiation alone (1.2%). However, since 2005, the use of combination therapy has increased significantly (16.1%). The rates of primary surgical resection and radiation therapy remain relatively unchanged. The longest survival has been observed among ATRT patients receiving combination therapy (5.9 ± 0.7 years). Multivariable analysis identified only distant metastases (OR 4.6) as independently associated with increased mortality, whereas combination therapy (OR 0.4) was associated with reduced mortality [53].

ATRTs were first described in the 1987 but were not recognized as a separate tumor entity by the World Health Organization (WHO) until 1993 [48], when they were classified as an embryonal grade IV neoplasm [49]. ATRT is now defined by alterations of either INI1 or, very rarely, BRG1 [30, 44, 106]. These alterations can be evaluated using immunohistochemistry for the corresponding proteins, with loss of nuclear expression correlating with genetic alteration.

Under the revised WHO 2016 Classification, the diagnosis of ATRT requires confirmation of the characteristic molecular defect. If a tumor has histological features of ATRT but does not harbor either of the diagnostic genetic alterations, only a descriptive diagnosis of CNS embryonal tumor with rhabdoid features can be made [57, 59].

Clinical Presentation

ATRTs arise in infratentorial or supratentorial locations in almost equal proportions and rarely arise in the spine [4, 51, 101]. The clinical presentation of ATRT depends on the age of onset and the location of the tumor. Because ATRT grows rapidly, patients typically have a fairly short history of progressive symptoms, measured in days to weeks.

Children younger than 3 years usually present with non-specific symptoms and signs such as vomiting, lethargy, irritability, weight loss, enlarging head circumference, and failure to thrive. Older patients commonly present with increased intracranial pressure or localizing signs. Cranial nerve palsies, headache, and hemiplegia are common [73, 81, 82]. They may also develop ataxia or regression of developmental milestones.

Diagnostic Imaging (Fig. 1)

Among 116 ATRTs in the European Rhabdoid Registry (EU-RHAB), 49% were located within the cerebellum or fourth ventricle, 34% were located in the hemispheres, 4% were located in each of the mesencephalic and pineal regions, 1.7% were found in the spine, and 6% crossed anatomic borders such that origin could not be determined [22].

Imaging features have often been considered non-specific [73, 103]. Parmar et al. [73] demonstrated that lesions are commonly large at presentation, with moderate-to-marked surrounding edema.

In the earlier literature, ATRTs were described as occurring more commonly in the infratentorial region, although this has not been reported in more recent series. Warmuth-Metz et al. [103] described preoperative imaging examinations of 33 patients with ATRT. In their series, supratentorial tumors were more frequent than infratentorial tumors in accordance with some of the largest series evaluating treatment and outcome in ATRT [34, 96]. Supratentorial tumors and those affecting both compartments were significantly larger than those in the infratentorial area. Fifteen percent of their patients showed meningeal dissemination at diagnosis, and this was significantly correlated with a younger age.

Most (52%) of the tumors were surrounded by some edema. Cysts or necrosis was present in 75% of tumors. Cysts in a peripheral position between the solid part of the tumor and the normal brain were seen in 39% patients, with an even distribution between the infra- and supratentorial compartments. This feature seems to be a regular finding in ATRTs [103]. On CT scan, ATRTs are solid or mixed lesions. The solid portion is commonly hyper-dense on non-enhanced CT, a feature attributed to the tumor's high cellularity and high nuclear-to-cytoplasmic ratio [73, 103].

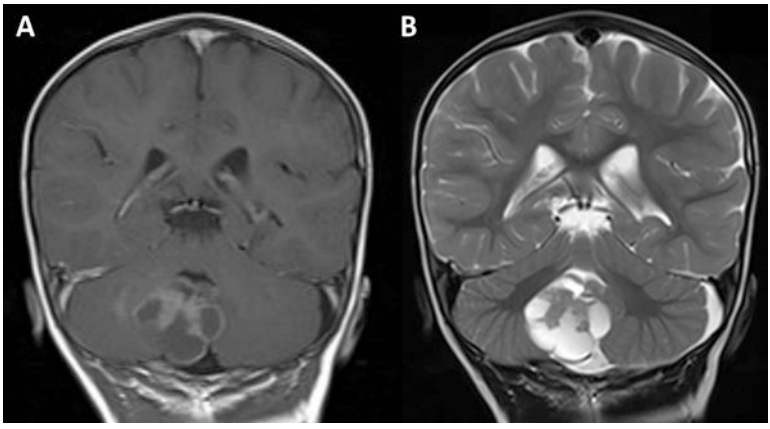

Fig. 1 Seventeen month male with a 3.5 cm atypical teratoid/rhabdoid tumor, localized to the right cerebellar hemisphere with a central solid component and several cystic loculations. (**a**) T1 post-gadolinium. (**b**) T2-weighted image

On MRI, signal intensity values on T1- and T2-weighted MR images vary widely [103]. An example is provided in Fig. 1. Parmar et al. [73] found that greater than 50% of these tumors revealed iso-intensity on T1-weighted images and more than 80% were either hypo-intense or heterogeneous on T2-weighted images. Moderate-to-marked enhancement with gadolinium was seen in all tumors. All intra-axial tumors showed extensive vasogenic edema. Hemorrhage was seen in 46% of patients [73, 103], calcification in 36%, necrosis in 46%, and cysts in 18%. These tumors also had a high propensity for subarachnoid dissemination, with 46% showing the presence of leptomeningeal metastasis at the time of presentation [73].

Parmar et al. [73] recommend that contrast-enhanced MR imaging of the brain and spine should be undertaken at the time of presentation and on follow-up because of the high rate of recurrence and leptomeningeal spread. Similar to most malignancies, ATRT cannot be reliably distinguished from other malignant brain tumors based on clinical history or radiographic evaluation. Surgery is necessary to obtain tissue to confirm the diagnosis of ATRT.

Tumor Pathology (Fig. 2)

Macroscopically, ATRTs are soft, pinkish-red, often well-circumscribed tumors with areas of necrosis and hemorrhages. These tumors arise in the cerebellopontine angle and variably infiltrate cerebellum and brainstem. ATRTs consist of heterogeneous cells with various morphological appearances [81]. Small undifferentiated embryonal cells are the most common tumor cell population, characterized by high nuclear/cytoplasmic ratio. They often contain a vesicular nucleus and a single nucleolus and show less nuclear hyperchromasia than cells of primitive neuroectodermal tumors (PNETs). Small groups or scattered rhabdoid cells typically with eccentrically placed nucleus, large eosinophilic nucleolus, abundant eosinophilic

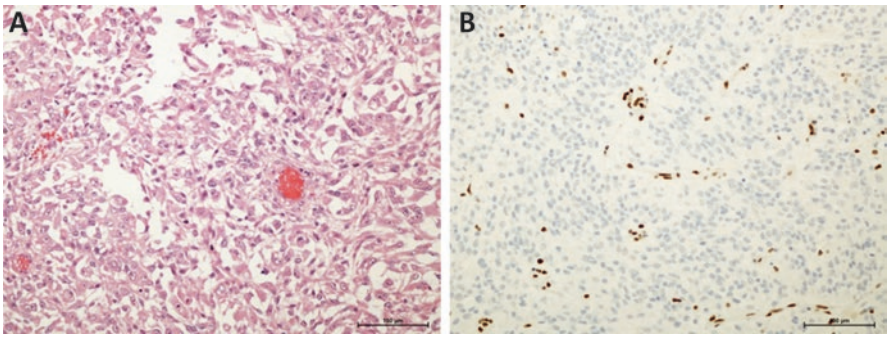

Fig. 2 (**a**) Rhabdoid component of an atypical teratoid/rhabdoid tumor. (**b**) Diagnostic loss of nuclear expression of INI1 in tumor cells, in contrast to INI1 expression in endothelial cells (serve as internal positive controls)

cytoplasm, and eosinophilic globular "ball-like" cytoplasmic inclusion are encountered in most ATRTs (Fig. 2a) but may be absent. In only a minority of ATRTs are rhabdoid cells the predominating component. Cells with glial, neuronal, epithelial, or mesenchymal features are observed in most tumors [63]. Occasionally, multinucleated or pleomorphic giant cells are noted. The mitotic and proliferative index is markedly increased, in particular in pediatric ATRTs. Zonal necrosis and hemorrhage are common. Characteristically, a fine fibrovascular network is present within the tumor, but microvascular proliferation may occur.

By immunohistochemistry, expression of glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), smooth muscle alpha-actin (SMA), and vimentin is found most consistently. Often, small groups or scattered tumor cells are immunopositive for synaptophysin, microtubule-associated protein 2 (MAP2), neurofilament protein (NFP), desmin, cytokeratins, and HMB-45. ATRTs lack nuclear expression of INI1, the SMARCB1 gene product, in contrast to normal tissue ([45]; Fig. 2b) and most other tumors, in particular PNETs, polymorphous gliomas, or rhabdoid meningiomas. ATRTs with retained INI1 expression but with loss of nuclear expression of BRG1, the SMARCA4 gene product, are rare.

Cribriform neuroepithelial tumor (CRINET) also lacks nuclear INI1 expression but shows no rhabdoid tumor component. This rare tumor is morphologically characterized by cribriform strands and trabeculae of epithelial cells [32]. Molecular findings of CRINETs including the methylation pattern are similar to those seen in the molecular ATRT-TYR subgroup, but the morphological appearance of the CRINET tumor cells and the cribriform architecture are different [39]. Diagnosis of CRINETs is important since these tumors may have a favorable prognosis.

Molecular Genetics and Biology

In order to specifically target ATRT with novel therapeutics, it is important to clearly understand the driving molecular mechanisms. In ATRT, recent analysis has elucidated recurring mutations in genes for components of the chromatin remodeling complex, SWItch/sucrose nonfermentable (*SWI/SNF*), in patients with ATRT, with *SMARCB1* being most commonly mutated, followed rarely by *SMARCA4* [22, 31, 55]. Both *SMARCB1* and *SMARCA4* are essential components of the *SWI/*SNF complex, which is important for lineage specification, maintenance of stem cell pluripotency, and gene regulation [38, 39, 104]. The SWI/SNF complex has important functions in neural development [108].

ATRTs are associated with mutation or inactivation of the *INI1/hSNF5/BAF47* tumor suppressor locus on chromosome 22q11.23 in almost all cases [79, 100]. ATRT is characterized by the biallelic loss of *SMARCB1* expression [81]. Up to 35% of patients with CNS rhabdoid tumors have germline *SMARCB1* alterations and a rhabdoid tumor predisposition syndrome characterized by the development of multiple rhabdoid tumors [8, 17, 85]. The majority of germline mutations occur de novo, and transmission across generations is rare [3, 23].

Although findings from small patient cohorts suggest molecular heterogeneity may underlie the clinical spectrum seen in ATRT tumors, cumulative genomic analyses, including whole exome sequencing studies, have shown *SMARCB1* loss as the only recurrent genetic event in ATRT [47, 55]. Reconciling clinical heterogeneity with tumor biology has been challenging, because it is a rare disease and there have been few biological and clinical studies [9], especially ones which studied CNS ATRT independently from non-CNS rhabdoid tumors [99].

Despite the absence of recurring genomic alterations beyond *SMARCB1* (and rarely other SWI/SNF complex members such as SMARCA4), biologically distinctive subsets of ATRT have been identified [38, 39, 99]. Torchia et al. [99] identified two molecular subgroups of ATRT with distinct features. Then, Johann et al. [38, 39] identified three distinctive subsets of ATRT, associated with differences in demographics, tumor location, and type of SMARCB1 alterations through the use of DNA methylation arrays and gene expression arrays [38, 39]. Johann et al. [38] termed these subsets ATRT-TYR, ATRT-SHH, and ATRT-MYC.

The recent transcription and methylation profiling studies by Torchia et al. [99] support the existence of at least two different molecular subgroups, groups 1 and 2 [99]. These tumors may be further stratified into average-, high-, and very high-risk groups by integration of tumor molecular subgrouping and clinical prognostic factors. They defined group 1 ATRTs as those most highly enriched for genes involved in the brain or neural development and axonal guidance and demonstrated upregulation of genes involved in the *NOTCH* developmental signaling pathway. The genes *FABP7* and *ASCL1*, markers of primitive neural lineage, were among the most highly upregulated genes [65, 87]. The *HES5/HES6* and *DLL1/DLL3* genes, which are also involved in the *NOTCH* pathway, were also highly enriched in group 1 ATRTs [14]. Torchia et al. [99] found that as a group-specific marker, *ASCL1* showed robust immunostaining and allowed for distinction between *ASCL1-positive* and *ASCL1-negative* tumors. *ASCL1* expression correlated with superior overall survival (OS), but not with progression-free survival (PFS), for all patients treated with chemotherapy [99].

In group 2 ATRTs, neural lineage marker expression was significantly decreased. Instead, these tumors have enrichment of genes involved in mesenchymal differentiation and the bone morphogenetic protein (BMP) signaling pathway including *BMP4*, *BAMBI*, *SOST*, *SERPINF1*, *FBN2*, and *MSX1* loci [99]. These tumors were significantly associated with infratentorial location, in contrast to group 1 ATRTs which were mostly supratentorial. In a small cohort of patients who did not receive radiation as part of their primary therapy, *ASCL1*-positive group 1 tumors correlated significantly with higher 5-year PFS and 5-year OS relative to the *ASCL1*-negative group 2 tumors. On univariate analysis, it was noted that *ASCL1* expression and not supratentorial tumor location was a significant prognostic factor for both PFS and OS in non-irradiated children [99].

The ATRT-TYR subset represented approximately one-third of cases and was characterized by elevated expression of melanosomal markers such as *TYR* (the gene encoding tyrosinase), *MITF*, or *DCT*. TYR is highly expressed in almost every case in this subgroup, hence the designation *ATRT-TYR*. Cases in this subset were

primarily infratentorial, with most presenting in children aged 0–1 years and 77% showing chromosome 22q loss, which was only seen in 20% and 12% of ATRT-SHH and ATRT-MYCN tumors, respectively.

The ATRT-SHH subset represented approximately 40% of cases and was characterized by elevated expression of genes in the sonic hedgehog (SHH) pathway such as *GLI2* and *MYCN*. Cases in this subset occurred with near equal frequencies in supratentorial and infratentorial regions. While most presented before age 2 years, approximately one-third of cases presented between 2 and 5 years.

The ATRT-MYC subset represented approximately one-fourth of cases and was characterized by elevated expression of MYC. They tended to occur in the supratentorial region. While most ATRT-MYC cases occurred by age 5 years, this subset represented the most common subset diagnosed at age 6 years and older. Focal deletions of *SMARCB1* were the most common mechanism of SMARCB1 loss for this subset.

Despite few differences between the ATRT subgroups at the genetic level, there were remarkable epigenetic differences. Both *ATRT-TYR* and *ATRT-SHH* revealed genome-wide hypermethylation, particularly in promoter regions. *ATRT-MYCN* showed hypomethylation. These differentially methylated regions have a large impact on the expression of genes located within them, including tumor suppressor genes (which are silenced) and oncogenes (which are activated) in regions where the partially methylated domain is absent. *SMARCB1* expression should be evaluated in all young patients with embryonal tumors to confirm the diagnosis of ATRT rather than medulloblastoma or other CNS PNETs.

Therapy and Prognosis

Survival rates for patients with ATRT are generally poor but have improved over recent years due to the development of clinical trials specifically designed for ATRT with stringent inclusion and exclusion criteria and a renewed focus on the vulnerability of affected young patients [28]. To date, no standard of therapy for ATRT has been defined. A significant proportion of ATRTs arise in children younger than 3 years. Treatment with conventional postoperative chemotherapy alone results in less than 20% survival [27, 29, 96]. Small cohorts of patients treated with ATRT-specific regimens have achieved survival rates greater than 50% [13, 96]. Improved survival has also been demonstrated for patients with gross total resection [13, 51].

Most recent treatment strategies recommend maximal safe surgical resection followed by intensive chemotherapy with or without intrathecal chemotherapy and focal or craniospinal radiation. However, treatment depends on the location of the tumor, initial staging, and age of the patient at presentation. The management of ATRT with conventional chemotherapy has been consistently associated with very poor outcomes, and most series have supported the benefit of aggressive multimodal therapy [51, 78]. While a multimodal approach that combines maximal safe resection, craniospinal irradiation, and intensive chemotherapy is considered optimal for long-term cure, the young age of many patients and/or involvement of critical structures within the CNS limits this approach [38, 39, 91].

In recent years, treatment approaches in Canada have been more homogeneous and based on the use of high-dose chemotherapy [51]. Treatment factors that predict survival have included the use of multimodality regimens containing radiotherapy, intrathecal chemotherapy, and/or high-dose therapy with stem cell rescue [4, 13, 26, 51, 96]. The series of patients investigated by Lafay-Cousin et al. [51] highlights the encouraging results associated with the use of high-dose chemotherapy and describes a proportion of long-term survivors (50%) who did not receive radiation. Novel therapy that improves outcomes while it decreases toxicity is greatly needed. As ATRT is typically a tumor of infancy, radiation-free approaches are often used in patients to minimize long-term neurodevelopmental sequelae [99]. Current curative therapy for ATRT is perhaps excessively toxic, including the acute toxicity of high-dose chemotherapy [26] and long-term toxicity of radiotherapy in young children. A major focus of current research is on the development of more focal, and potentially less harmful, methods of radiotherapy, such as proton beam radiation.

Data from a small cohort by Torchia et al. [99] suggests that children with localized supratentorial ATRT, with high *ASCL1* expression and complete surgical resection, represented a favorable-risk category with a projected 5-year PFS and OS of 60%, with disease recurrence in only about 33% of patients [99]. This will have to be validated in future trials. Ongoing, prospective studies will more precisely define the outcome of children with ATRT in the current era.

Future Considerations

The availability of ATRT cell lines and accurate preclinical mouse models have enhanced the discovery of novel therapeutic targets for ATRT. Current targets under consideration are aurora A kinase, cyclin D1, EZH2, and insulin-like growth factor-1. The availability of aurora A kinase inhibitors has facilitated the development of a phase II trial for patients with recurrent ATRT and malignant rhabdoid tumor (NCT02114229). If this trial demonstrates the efficacy of this agent, it will most likely be incorporated into therapy for patients with newly diagnosed ATRT [24]. Results from Torchia et al. [99] suggest that inhibitors of *NOTCH*, *BMP*, and MAPK signaling and angiogenesis would be important novel, subgroup-specific therapeutic agents for ATRT [99].

Pilocytic Astrocytoma

Epidemiology

Pilocytic astrocytomas (PAs) are a distinct histologic and biologic subset of gliomas and account for 5% of all gliomas. PAs are typically well-circumscribed WHO grade I tumors that have a slow growth rate. PA is the most common primary brain tumor in 0- to 19-year-olds. Pilocytic astrocytoma accounts for 15% of children and adolescents (0–14 years) and 18% of childhood (0–14 years) primary brain tumors [10].

Clinical Presentation

Pilocytic astrocytomas arise throughout the CNS, although most frequently occur in the cerebellum (42%), followed by the supratentorial compartment (36%), the optic pathway and hypothalamus (9%), the brainstem (9%), and the spinal cord (2%) [10]. A rare variant termed "pilomyxoid astrocytoma" occurs predominantly in children under 1 year of age, in the hypothalamic/chiasmatic region. Pilomyxoid astrocytoma was categorized as WHO grade II in the 2007 WHO Classification due to reports of an increased likelihood of recurrence, but tumor grading for this entity has been omitted in the 2016 update [57, 59].

The presentation of PAs is generally insidious in onset due to the slow growth of the tumor. Identification of early symptoms is dependent on tumor localization and the ability of the patient to communicate neurological change. Cerebellar tumors commonly present with ataxia, cranial nerve defects, and signs of increased intracranial pressure (headache, nausea, and vomiting).

Diagnostic Imaging (Fig. 3)

Neuroimaging in PA is used to determine the size and the site of origin of the lesion, establishing a primary diagnosis. PA is easily imaged on both CT and MR imaging. On CT images, PAs classically present as a mass with both a solid and cystic component. The solid component usually enhances with contrast, and the cyst wall has variable enhancement. The appearance of a cyst with a mural nodule is almost pathognomonic for PA. On MR imaging, the cystic and solid components are better appreciated. PAs are typically hypo- or iso-intense on T1-weighted sequences and hyperintense on T2-weighted or FLAIR sequences ([2]; Fig. 3).

Tumor Pathology (Fig. 4)

Pilocytic astrocytomas (PAs), WHO grade I, are macroscopically soft, gray, often mucoid, and well-demarcated tumors. Many cerebellar PAs form cysts within or adjacent to the tumor, with a contrast-enhancing solid mural nodule, similar to hemangioblastomas and gangliogliomas. These cysts contain clear, yellow, or brown protein-rich fluid and are often demarcated by a compressed tumor area with variable fibrous changes.

Histopathologically, PAs characteristically have a biphasic architecture, composed of a loosely textured microcystic and a compact fibrillary component (Fig. 4a). The microcystic component contains astrocytes with short multipolar process, whereas the astrocytes of the fibrillary component have uni- or bipolar hairlike ("piloid") processes. Rosenthal fibers, amorphous sausage-like eosinophilic struc-

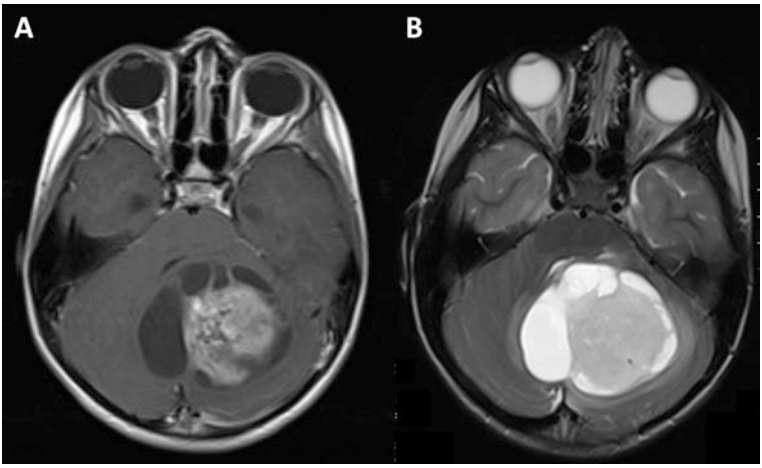

Fig. 3 Four-year-old with a large 5.4 × 5.8 × 5.2 cm mass, a pilocytic astrocytoma located in the left cerebellum with extension across the vermis into the medial aspect of the right cerebellar hemisphere. (**a**) T1 post-gadolinium. (**b**) T2-weighed image

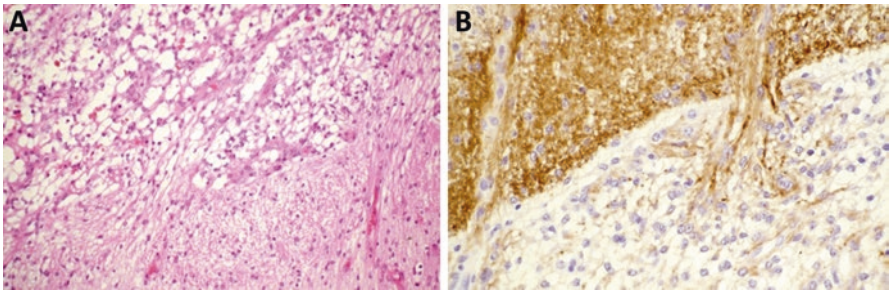

Fig. 4 (**a**) Pilocytic astrocytomas are characterized by a biphasic tumor architecture, with a solid fibrillary and a loose microcystic component (H&E). (**b**) Strong expression of the astrocytic marker glial fibrillary acidic protein (*GFAP*) is present in bipolar tumor cells of solid fibrillary areas in contrast to multicystic tumor cells of microcystic areas

tures, are more frequent in the fibrillary component but may be absent. Eosinophilic granular bodies (EGBs), proteinaceous material positive in periodic acid Schiff (PAS) stain, are present in the multicystic component of some PAs. Both structures can be found in other neoplasms and in nonneoplastic lesions. Many PAs are rich in vasculature, most often hyalinized vessels are present, but serpentlike microvascular proliferations with glomeruloid vessels are also frequent. Often, these glomeruloid proliferations are lining the tumor cyst wall. Some classical PAs show zonal, ischemic-like necrosis. Neither the presence of necrosis, of microvascular proliferations, nor of degenerative features such as nuclear hyperchromatism, pleomorphism, and pseudoinclusions indicate a worse prognosis. Rare mitotic figures may be present in classical PAs. Diffuse brisk mitotic activity, usually defined as >4 mitotic

figures per 10 high-power fields, indicates anaplastic change and has prognostic implications [80]. Necrosis is often present but not associated with anaplasia. The prognosis of these *anaplastic pilocytic astrocytomas* is better than in glioblastomas.

Classical PAs are well-circumscribed tumors which typically show only focal infiltration of surrounding brain tissue. In contrast, some PAs mimic diffusely infiltrating astrocytomas by morphology, tumor architecture, and infiltration behavior but have a much better prognosis than diffusely infiltrating astrocytomas. This *diffuse "variant" of pilocytic astrocytomas* (dPAs) has a similar prognosis compared to classical PAs [33], and approximately 50% harbor the most common BK fusion variant [35]. Thus, molecular findings and biological behavior suggest that classical PAs and dPAs represent a single tumor entity. Diffuse astrocytomas account for approximately 15% of all cerebellar astrocytic tumors, but most are high-grade astrocytomas. Particularly cerebellar PAs often show infiltration of leptomeninges with focal desmoplasia, a finding that does not predict subarachnoid dissemination or CSF spread and does not affect prognosis.

Pilomyxoid astrocytoma (PMA) is typically found in the hypothalamic region but rarely occurs in cerebellar location. PMA is characterized by monomorphous bipolar tumor cells, often in angiocentric arrangement, and myxoid tumor matrix [97]. PMAs are associated with a more aggressive clinical course; thus, these tumors were assigned to WHO grade II in the 2007 CNS tumor classification. However, the tumor grade for PMA has been reconsidered in the subsequent upgrade [57].

PAs characteristically show strong immunoreactivity for glial fibrillary acidic protein (GFAP), S100, and OLIG2. The bipolar tumor cells of compact areas are strongly immunopositive for GFAP, whereas multipolar tumor cells show weaker expression (Fig. 4b). Rosenthal fibers are often GFAP immunopositive in their fibril-rich periphery. Weak expression of synaptophysin may be present in occasional PAs and PMAs.

Molecular Genetics and Biology

Molecular classification of PAs has been slowly evolving since 2008. High-throughput genetic sequencing and gene expression profiling have made information regarding the biologic processes necessary for tumor growth and a molecularly based approach to therapy possible. Alterations in the RAS/RAF/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway are found in the majority of PAs [40, 93].

The most common genetic alteration found in PAs is the tandem duplication at 7q34, which produces a fusion between two genes, *BRAF* and *KIAA1549*. This "B-K" gene fusion occurs in up to 70% of PAs and is most frequent in cerebellar tumors (72–98%) and less frequent in the other sites such as the optic pathway (43–69%) [6, 7, 36, 40]. The N-terminal end of KIAA1549 replaces the N-terminal end of BRAF, producing a constitutively activated BRAF kinase domain and activa-

tion of the Ras/ERK pathway [7, 21, 42, 89]. The fusion protein can be derived from at least nine different fusion site combinations, with the most common fusion between *KIAA1549* exon 16 and *BRAF* exon 9 [41, 110]. Other gene fusions leading to constitutively active BRAF protein fusion products have also been described in PAs, including FAM131B, RNF130, CLCN6, MKRN1, GNA11, QK1, FZR1, and MACF1 [15, 21, 41, 75, 110].

Activating gene mutations have also been described in a subset of PAs (2–9%). The $BRAF^{V600E}$ mutation results in constitutively active BRAF protein. This mutation, unlike the *KIAA1549-BRAF* fusion protein, is *not* specific to PAs [7, 43, 84, 89]. The *BRAFinsT* mutation has also been described in PA in up to 3% of tumor samples specifically in the young adult population [18].

Multiple additional genetic alterations have been described in PAs. *KRAS* somatic mutations occur at low frequency (3–5%) [16, 24]. Aberrations affecting *FGFR1*, including point mutations (P.N546K, P.K656E), FGFR1-TACC1 fusions, and internal tandem duplications, have been identified [41, 90, 110]. NTRK family receptor kinase mutations have also been reported at a low rate, due to gene fusions leading to kinase activation [41, 110]. FGFR1 alterations are more frequent in midline structures, whereas BRAF V600 and NTRK family fusions are more frequent in supratentorial tumors [52, 88, 95]. There is unknown significance of reported 41% of PAs having MYB protein upregulation. Genomic alterations of MYB have only been found in diffuse gliomas [93].

PAs, particularly optic pathway tumors, occur in up to 20% of neurofibromatosis type 1 (NF1) patients. NF1 is an autosomal dominant syndrome due to mutations in the *Nf1* tumor suppressor gene leading to an increase in the active form of Ras and constitutive activation of the Ras/ERK signaling pathway [5, 16, 54, 55, 86]. In general, patients with NF1-associated PAs have a more indolent course and are less likely to require treatment.

Epigenetic analysis revealed a hypomethylation signature specific to PA that included many differentially methylated developmental genes and suggests aberrant expression of developmental regulatory processes as a genetic cause of PA [37, 52]. Both transcriptome and methylome analyses revealed a distinctive pattern for infratentorial versus supratentorial PA [52, 88, 95].

Therapy and Prognosis

Overall, PA has an excellent prognosis with 10-year survival over 90% [10]. The treatment is primarily surgical, and prognosis depends on the completeness of the resection. Patients who undergo subtotal resection are often treated with chemotherapy and/or radiation therapy at tumor progression to improve long-term survival. Chemotherapy following low-grade glioma protocols is the preferred option for younger patients due to the long-term sequelae of radiation in the developing neuroaxis [76]. Infrequently major postoperative sequelae occur, such as postoperative posterior fossa mutism syndrome (<5% of patients) or marked new brainstem

or cerebellar deficits [66]. More commonly, mild fine motor or balance issue occurs but often does not interfere with activities of daily living. Long-term survivors usually have close-to-normal academic achievement, and measures of quality of life are usually normal [1, 111].

Future Considerations

Although targeted therapies are unlikely to become the standard of care for newly diagnosed PA, identification of the BRAF V600E mutation suggests a poorer prognosis, and these tumors may respond to BRAF inhibitor therapies, such as with vemurafenib and dabrafenib [11]. Furthermore, since resistance to BRAF inhibitors is often encountered, combination with a MEK inhibitor may be beneficial [20]. Future clinical trials will incorporate molecular genetic tumor profiling, and targeted therapies will be carefully integrated [70].

Ependymoma

Epidemiology

Ependymomas are primary tumors in the CNS and account for 10% of childhood brain tumors and about 30% of tumors in children less than 3 years of age [58, 61]. The majority of ependymomas are seen in children less than 7 years old, with 25–51% of cases in children under 3 years of age. A second peak is observed in adults in the third to fifth decades, although the histologic subtypes and neuroanatomic compartments vary considerably between children and adults. Ependymomas originate from the radial glial stem cells and therefore can occur at any site along the ventricular system and in the spinal cord [94]. The anatomical distribution varies according to age, supratentorial compartment and spinal cord being more common sites in older children and adults, with infratentorial locations more frequent in infants and children [58]. Overall, supratentorial tumors account for one-third, whereas posterior fossa tumors, including the cerebellum, account for two-thirds of ependymomas.

Clinical Presentation

The presentation of ependymoma depends on the location of the tumor, and often, due to slow growing nature of the tumor, onset of symptoms and signs can be insidious. Posterior fossa lesions present with symptoms of raised intracranial pressure,

such as headache, nausea and vomiting, ataxia, vertigo, and papilledema. Cranial nerve palsies are also common, involving cranial nerves VI–X. When tumors arise in the supratentorial compartment, seizures or focal neurologic deficits may be present. Tumors involving the spinal cord present with deficits due to compression of nerve roots or ascending/descending nerve tracts and are related to the anatomical level of the tumor.

Diagnostic Imaging (Fig. 5)

Imaging in ependymomas, similar to other CNS tumors, is used to establish a primary diagnosis and determine the size and site of origin of the lesion. Ependymoma can be imaged using both CT and MRI. On CT, the tumors are usually isodense to the brain parenchyma and may have calcifications in up to 50% of cases [12]. On T1-weighted MR imaging, ependymomas are usually hypo-intense or iso-tense to normal gray matter and heterogeneously enhance after contract administration. On T2-weighted images, they are typically isodense or slightly hyperintense to normal gray matter. Foci of signal heterogeneity representing methehemoglobin, hemosiderin, necrosis, calcification, encased native vessels, or tumor vascularity are commonly seen [12] (Fig. 5). It is important to image the entire craniospinal axis, as neuroaxis dissemination can occur in 3–11% of cases [74].

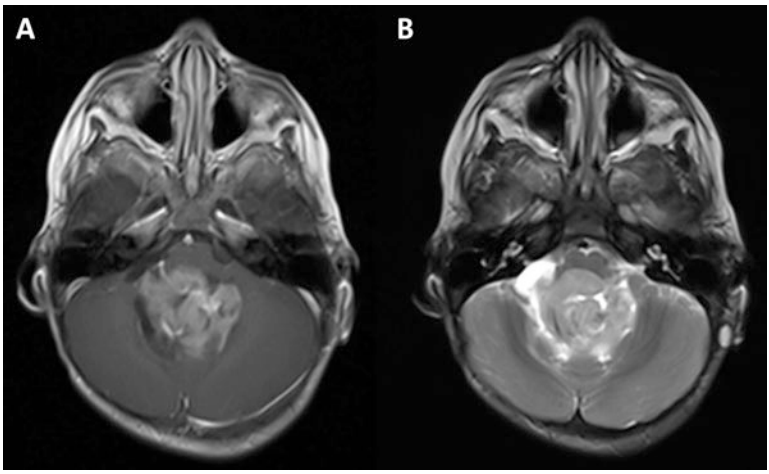

Fig. 5 Fifteen month male with ependymoma with cystic and solid components localized to the fourth ventricle measuring 3.9 × 3.4 cm. (**a**) T1 post-gadolinium image. (**b**) T2-weighted image

Tumor Pathology (Fig. 6)

Ependymomas are well-circumscribed, soft, occasionally cystic, tan-colored tumors that most often arise from the fourth ventricle in the posterior fossa. Commonly, they extend through the foramina of Luschka and Magendie into the cerebellopontine angle and basal cisterns where they often enclose cranial nerves and vessels.

Histopathologically, ependymal tumors are sharply demarcated and present with a wide spectrum of cell morphology but share key features: pseudorosettes are perivascular arrangements of tumor cells which fibrillary cell processes create perivascular anuclear zones (Fig. 6a). True ependymal rosettes are composed of mostly cuboidal tumor cells with a central lumen.

Classic ependymoma (WHO grade II) is characterized by small uniform tumor cells with round-to-oval nuclei in variable cell density. In some ependymomas, nodules of high tumor cell density are present, often associated with an increased mitotic activity. Pseudorosettes are a typical feature of ependymomas, whereas true ependymal rosettes are seen in ~25%. Hemorrhages and dystrophic calcifications are often observed. Other morphological variants include *papillary*, *clear cell* [83], and *tanycytic ependymomas* (WHO grade II) which occur less often in the posterior fossa.

Anaplastic ependymoma (WHO grade III) is defined by a high cell density, high mitotic activity, microvascular proliferation, and necrosis, but the association between histological grade and clinical outcome is controversial. Age of the patient and anatomical site of the tumor appear to be more reliable prognostic factors in ependymomas.

Immunohistochemically, the vast majority of ependymomas express S100, vimentin, glial fibrillary acidic protein (GFAP), and epithelial membrane antigen (EMA). Expression of GFAP is typically present on the luminal surface of true ependymal rosettes and in the perivascular anuclear zones of pseudorosettes. Many ependymomas show dot- or ringlike cytoplasmic immunopositivity for EMA (Fig. 6b). In contrast to supratentorial ependymomas, expression of L1CAM, which indicates rearrangement of *C11orf95*, is not detectable in posterior fossa ependymomas.

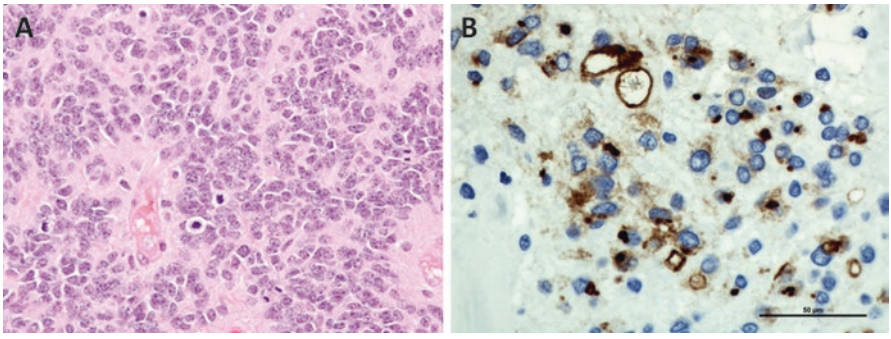

Fig. 6 (**a**) Anaplastic ependymoma, WHO grade III, with markedly increased mitotic activity. Five mitotic figures are seen in this high-power field. (**b**) Cytoplasmic dot- and ringlike immunoreactivity for epithelial membrane antigen (EMA) in an anaplastic ependymoma

Molecular Genetics and Biology

Risk stratification based on histological categorization is difficult in ependymomas, and variability has been seen in outcomes despite similarities in microscopic characteristics. Therefore, molecular analysis has been undertaken to elucidate the pathogenesis of these tumors. In genomic studies, supratentorial ependymomas have been found to have genomic clustering in the region of chromosome 11q12.1–q13.3. This region undergoes gross interchromosomal and intrachromosomal rearrangements, leading to the fusion of the poorly characterized gene *C11orf95* and *RELA*, a downstream target of NF-κB, an important regulator of cell maintenance. This rearrangement has been found in up to 70% of supratentorial ependymomas [72]. A second recurrent gene fusion product, *Cllorf95* and *YAP1*, has also been described predominantly in the younger age group and appears to have a favorable survival outcome, although further studies need to occur to elucidate its role in tumorigenesis [71].

Posterior fossa ependymomas have also been studied in genomic analyses, leading to the transcriptional profiles of posterior fossa (PF) group A (PFA) and group B (PFB) ([105]; Table 3). PFA patients are usually younger, with tumors located laterally and extending to the cerebellopontine angle. Overall PFA tumors are more aggressive in nature and are associated with poor outcomes. These tumors demonstrate relatively stable cytogenetics, although up to 25% of PFA ependymoma has a gain of chromosome 1q, correlating with a poor prognosis [60, 71]. Upregulation of multiple cancer-related signaling pathways has been observed, although they are not specific to ependymomas, including PDGFR, EGFR, VEGF, MAPK, and TGFβ [102, 105]. Epigenetic modification, specifically hypermethylation, has also been demonstrated in PFA tumors. The genes that are CpG methylated in PFA ependymomas are similar to the genes that are silenced by the polycomb repressive complex 2 (PRC2) in embryonic stem cells. PRC2 controls all forms of methylation of lysine 27 on histone H3 and is responsible for silencing genes involved in cell differentiation and tumorigenesis [19, 67].

PFB ependymomas often arise in older patients, occur more frequently in the midline, and are less likely to metastasize. PFB tumors demonstrate greater copy number variation with gain of chromosome 9, 15q, and 18 or loss of chromosome 6q and 22q. These cytogenetic abnormalities have been associated with improved

Table 3 Posterior fossa ependymoma summary

	PF-A	PF-B
Age group	Children	Adults and older adolescents
Gender	M>F	M<F
Prognosis	Poor	Good
Molecular genetics	Epigenetic modification, LAMA-2 expression	Chromosomal modification, NELL2 expression
Histopathology	Anaplastic ependymoma, WHO grade II/III	Anaplastic ependymoma, WHO grade II/III

prognosis [50, 105]. PFB ependymoma does not demonstrate the epigenetic modifications and hypermethylation profiles when compared to PFA tumors.

An unsupervised gene clustering and multivariate analysis revealed a 10-gene signature that qualified as an independent predictor of recurrence-free survival in infratentorial ependymoma [102]. As a result of these key discoveries, novel therapeutic strategies can now be tested that target PRC2 and alter DNA methylation status in ependymoma [25].

Therapy and Prognosis

Overall the prognosis for ependymoma is relatively unsatisfactory with overall survival reported as 50–71%. Local control with surgical resection is clinically important as ependymoma is often locally invasive with low metastatic potential. Leptomeningeal dissemination is seen at diagnosis in only 7–12% of cases, and recurrent disease most frequently occurs at the primary tumor site [64]. Survival of patients with GTR ranges from 66% to 80%, compared to subtotal resection survival of 0–47%. Unfortunately, GTR can only be achieved in approximately 50% of cases due to tumor location and risk of unacceptable neurological injury, often requiring patients to be managed with a tracheostomy and/or gastric feeding tubes [62]. Postoperative involved field radiation therapy is standard of care for patients older than 1 year with non-disseminated ependymoma to lower the risk of local recurrence. Many children in the USA and other countries are being referred to treatment centers that offer proton radiotherapy instead of the more widely available photon-based delivery systems. The role of chemotherapy is less well established and is being investigated in clinical trials. The goal of chemotherapy is to defer radiation therapy in younger patients and as an adjunct for patients with residual disease to improve overall survival [56]. However, chemotherapy has not made a significant impact in this disease [46]. Relapsed ependymoma has an extremely poor prognosis with 5-year overall survival rate reported at 28%, with the median time to recurrence or progression distributed at 18–45 months [98, 109].

Future Considerations

The impact of chemotherapy as a therapeutic strategy to delay radiotherapy or permit “second look” surgery remains unclear. Although several phase II studies offering EGFR inhibitors and/or other receptor tyrosine kinase inhibitors to patients with recurrent, progressive ependymomas have been completed, results have been less than promising. Given the more common presentation of the genomically “bland” PFA tumors in childhood, epigenetically based therapies may hold more promise [46, 107].

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