Chapter 19

Cerebellar tumors

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Abstract

The cerebellum is the most common site of presentation of central nervous system tumors in children but exceedingly rare in adults. Children often present with acute symptoms related to increased intracranial pressure, requiring urgent surgical intervention. The differential diagnosis is broad and includes a variety of benign and malignant entities. Cerebellar low-grade gliomas are the most common and benign, slow-growing tumors, for which surgical resection alone is curative. Embryonal tumors, on the other hand – most commonly medulloblastomas – are highly aggressive and treatment includes intensive postsurgical radiotherapy and chemotherapy.

Driven by multiple genomewide profiling studies, the field of neuro-oncology is making great strides towards understanding how different tumors develop and embarking on a new generation of molecularly informed clinical trials.

INTRODUCTION

Central nervous system (CNS) tumors comprise a variety of benign and malignant neoplasms prevalent across the entire age spectrum (Louis et al., 2016). Though the overall incidence is higher in adults, brain tumors are the most common solid tumors and the leading cause of cancer-related death in children (Ostrom et al., 2016). Cerebellar tumors comprise the largest proportion of CNS tumors in children but are rare in adults. Regardless of age and histology, cerebellar tumors are critical lesions that often present with severe symptoms related to compression of the cerebellum and adjacent brainstem or obstruction of cerebrospinal fluid (CSF) flow, requiring urgent treatment.

Tumor- and treatment-related sequelae may have a profound impact on the neurologic outcome and quality of life of those affected. The developing CNS of young patients is especially susceptible to the deleterious side-effects of treatment, in particular radiotherapy (Packer, 2008; Moxon-Emre et al., 2014).

Over the past decades, a multitude of molecular profiling studies have led to an improved understanding of the genetic drivers underlying tumor development and are revolutionizing how we stratify, treat, and care for patients with cerebellar tumors.

EPIDEMIOLOGY

Across all ages, brain tumors represent only 2% of all cancers but account for an unequal high share of cancer-related morbidity and mortality. According to data from the Central Brain Tumor Registry of the United States – a registry that collects information on both benign and malignant brain tumors diagnosed in the United States – CNS tumors have an annual age-adjusted incidence of 5.47 per 100,000 population in children aged 0–14 years, representing the most common tumors and the leading cause of cancer-related death in this age group, with brainstem and cerebellar tumors causing the greatest proportion of deaths (37.9% and 16.6%, respectively) (Ostrom et al., 2015, 2016).
Among older adolescents and young adults (15–39 years) and those aged 40 years or older the age-adjusted incidence is 10.71 and 40.10 per 100,000 population, respectively.

The incidence of brain tumors has been increasing over the last decades (Modan et al., 1992; Smith et al., 1998; Hoffman et al., 2006). Though multiple environmental factors have been proposed to play a role, this increase is thought to be largely due to better detection since the introduction of magnetic resonance imaging (MRI) in the 1980s (Smith et al., 1998), the inclusion of nonmalignant entities in the main registries, and an aging population (Ostrom et al., 2016).

**ETIOLOGY**

With molecular profiling of somatic and germline events in patients with brain tumors, it has become apparent that hereditary factors are responsible for a higher than initially thought number of brain tumor cases, although much about the topic is still unknown. Germline mutations in cancer predisposition genes are estimated to occur in 8.6% of cases of CNS tumors in children and adolescents, but the probability is higher for certain types of tumors, such as medulloblastoma (MB: 13.5%), when compared to low-grade glioma (7.9%) or ependymoma (6.0%) (Zhang et al., 2015).

The correlation with environmental exposures has been extensively studied and thus far the only factor consistently found to be associated with increased risk of brain tumors in children is exposure to ionizing radiation (Shore et al., 1976; Relling et al., 1999). There are no significant data supporting a role of nutrition, parental exposure to electromagnetic fields, or mobile phone use in brain tumor development (Feychting et al., 2000; Lubin et al., 2000; Connelly and Malkin, 2007; Aydin et al., 2011).

**CLASSIFICATION AND PATHOPHYSIOLOGY**

With the advent of tumor molecular profiling, the classification of CNS tumors is undergoing major changes. Classification based on morphology alone has important shortcomings that have long been a matter of concern, such as lack of interobserver consistency, especially for ependymoma, astrocytoma, and mixed neural/glial tumors (Bruner et al., 1997; Ellison et al., 2011). The 2016 World Health Organization (WHO) classification incorporates several novel molecular markers to redefine brain tumor entities and formulates a novel approach to tumor diagnosis in the molecular era (Louis et al., 2016).

**Malignant cerebellar tumors**

**MEDULLOBLASTOMA**

MB is a malignant embryonal tumor of the cerebellum (Fig. 19.1), prevalent across the entire age spectrum but exceedingly rare in adults (< 1% of adult CNS tumors) (Ostrom et al., 2016). In children 0–14 years, MB is the most common embryonal brain tumor with an age-adjusted incidence rate of 0.49 per 100,000 (Ostrom et al., 2015).

There are four molecular subgroups of MB – wingless (WNT), sonic hedgehog (SHH), group 3 and group 4 – with distinct clinical features, cells of origin, pathogenesis, and outcome (Thompson et al., 2006; Cho et al., 2011; Northcott et al., 2011; Holgado et al., 2017). WNT MBs are thought to originate from dorsal brainstem progenitors of the lower rhombic lip and typically arise at the level of the cerebellopontine angle and cerebellar peduncle. WNT MBs account for 10% of MBs and display WNT pathway activation, commonly due to mutations in CTNNB1 gene encoding beta-catenin. With low propensity to metastasize and...
good response to different treatment regimens (overall survival > 90%), WNT tumors have the best prognosis of all four subgroups (Shih et al., 2014; Ramaswamy et al., 2016b).

SHH MBs originate from granule neural precursor cells in the external granule cell layer of the cerebellar cortex and arise laterally in the cerebellar hemispheres, whereas group 3 and group 4 tumors are located in the midline. SHH MBs have a bimodal age distribution, with peaks in infancy and adolescence/adulthood. Activation of the SHH pathway and multiple genetic drivers are characteristic of these tumors, such as PTCH mutations (seen across all age groups), SUFU mutations predominantly in infancy, TP53 mutations in school-aged children, and SMO and TERT mutations in older patients (Kool et al., 2014).

Mutations in PTCH may occur as well in the germline, associated with nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome. The prevalence of MB among patients with NBCCS is estimated to be around 4% (Evans et al., 1991; Hahn et al., 1996; Kimonis et al., 2004). A subset of patients with mutations in SUFU – another tumor suppressor gene on the SHH pathway – has concomitant germline mutations and loss of the wild-type allele, an NBCCS-like cancer predisposition syndrome that is associated with a higher risk of developing MB than PTCH-associated NBCCS (Taylor et al., 2002; Smith et al., 2014). About 40–50% of patients with TP53 mutations have germline mutations, associated with Li–Fraumeni syndrome. p53 mutated SHH MBs are highly aggressive tumors with a dismal prognosis (Zhukova et al., 2013). Interestingly, TP53 mutations in WNT MB have no prognostic implications.

Group 3 tumors (30% of all MB) are more common in young children and rare in adults and have a tendency to metastasize along the leptomeninges. Metastatic group 3 tumors have a very poor prognosis. Multipotent neural stem cells of the ventricular zone, precursors of all cerebellar GABAergic neurons, have been proposed as the cell of origin for group 3 tumors, which have GABAergic transcriptional signature. MYC overexpression is common and a subset of tumors has MYC amplification, which correlates with poor outcome (Grotzer et al., 2001; Shih et al., 2014).

Group 4 tumors are the most common (40% tumors) and overall have an intermediate outcome. The cell of origin remains unknown; common cytogenetic alterations include isochromosome 17q and amplification of MYCN. Loss of chromosome 11 and/or gain of whole chromosome 17 were found to be predictive of good prognosis in a retrospective study (Shih et al., 2014). The 2016 WHO classification of CNS tumors recognizes four genetically defined variants, additionally subdividing the SHH subgroup between SHH p53 WT and SHH p53 mutant (Louis et al., 2016).

**Ependymoma**

Ependymomas are derived from ependymal cells lining the ventricles or from the ependymal cell rests and account for 10% of posterior fossa tumors in childhood. They typically arise in the floor and may fill the entire fourth ventricle, with a tendency to extend through the foramina of Magendie or Luschka (Fig. 19.2) (Yuh et al., 2009).

Ependymal tumors are prevalent in children and adults but the histologic, molecular, and clinical characteristics are quite distinct between different ages. DNA methylation profiling of 500 ependymomas from all anatomic locations and ages expanded on previous studies and defined nine different subgroups, three of them of posterior fossa tumors: EPN_PFA, EPN_PFB, and subependymoma (Pajtler et al., 2015).

**Fig. 19.2.** Ependymoma (EPN-PFA). (A) Expansive lesion at the level of the medulla (B) extending inferiorly to the spinal canal up to the level of C2 (T2-weighted sequences).
Subependymomas are benign tumors seen exclusively in adults. Though ependymomas behave primarily as localized, slow-growing tumors, the majority of high-risk patients are children with EPN_PFA tumors, characterized by younger age (median age 3 years), high risk of recurrence, and presence of metastases at recurrence (Witt et al., 2011). EPN_PFB tumors are predominantly diagnosed in adults, whereas in children aged 10–17 years there is equal incidence of both subgroups (Pajtler et al., 2015; Ramaswamy et al., 2016a). Despite differences in clinical behavior, both EPN_PFA and EPN_PFB have a bland genome and low rate of mutations; EPN_PFA have increased in DNA methylation and epigenetic deregulation is thought to be the main driver of tumor development (Mack et al., 2014).

**ATYPICAL TERATOID/RHABDOID TUMORS**

CNS atypical teratoid/rhabdoid tumors (AT/RT) are highly aggressive embryonal tumors that are part of a group of malignancies – rhabdoid tumors – that may arise in other sites, most commonly the kidneys. AT/RTs are rare and typically occur in children under the age of 3 years (where they represent about 10% of tumors in this age group) but can also occur in older children and adults. About half of tumors arise in the posterior fossa and prior to being recognized as a separate entity were misdiagnosed as MB. Leptomeningeal metastatic seeding is seen in 20% of patients at time of diagnosis. Characterized by inactivating mutation or deletion of the tumor suppressor gene SMARCB1 on chromosome 22 (Versteege et al., 1998), up to 35% of patients with AT/RT have germline mutations. Decades after the identification of the genetic initiator of AT/RT, the pathogenesis of these tumors remains poorly understood. Recent studies have shown that AT/RTs comprise three epigenetic subgroups with distinct genomic profiles and SMARCB1 genotypes (Torchia et al., 2015, 2016).

**OTHER EMBRYONAL TUMORS**

The most recent 2016 WHO classification of CNS tumors reclassifies a group of tumors previously known as primitive neuroectodermal tumors (PNETs) and removed the term from the nomenclature. These tumors are rare and usually supratentorial but in about 10% of cases arise in the posterior fossa. The reclassification includes the C19MC-amplified ETMR tumor entity that comprises the majority of lesions previously known as ETANTR/ETMR (embryonal tumors with abundant neuropil and true rosettes, also known as embryonal tumors with multilayered rosettes). New brain tumor entities were recently proposed based on the molecular profiling of these tumors, two of which are described as well in the cerebellum: CNS high-grade neuroepithelial tumor with MNI alterations and CNS high-grade neuroepithelial tumor with BCOR alterations (Sturm et al., 2016). While research is ongoing, the 2016 WHO classification proposes CNS embryonal tumor, not otherwise specified (NOS) for tumors without specific molecular markers previously classified as CNS PNETs (Louis et al., 2016).

**Benign cerebellar tumors**

**pediatric low-grade gliomas**

Pediatric low-grade gliomas (PLGG) encompass a variety of benign tumors of glial origin that can arise anywhere in the CNS, most commonly (one-third of tumors) in the cerebellum (Guerreiro Stucklin et al., 2016; Krishnatry et al., 2016). The most common histology is pilocytic astrocytoma, characterized by the presence of cells with bipolar “hair-like” processes, low mitotic index, and the presence of Rosenthal fibers on histology (Fig. 19.3). Though PLGGs are often associated with genetic predisposition syndromes – most notably neurofibromatosis type 1 (15%) – the lesions in children with rofibromatosis type 1 are typically located in the optic pathway and...
cerebellar location is uncommon (Friedman and Riccardi, 1999). Glial tumors arising from the brainstem—including dorsally exophytic low-grade gliomas and the high-grade diffuse intrinsic pontine gliomas—may exhibit a pattern of growth extending into the cerebellar peduncles/cerebellar hemispheres.

A hallmark of PLGGs is activation of the Ras/MAPK pathway, frequently through alterations at the level of the BRAF oncogene. A gain of approximately 2 Mb at 7q34 was recognized as a defining feature of PLGG (Pfister et al., 2008) and found to correspond to duplication of the BRAF gene, associated with a fusion between the genes KIAA1549 and BRAF (Jones et al., 2008). The fusion causes loss of the autoregulatory N-terminal domain and constitutive activation of BRAF. BRAF-KIAA1549 fusions are present in two-thirds of PLGGs and common in PLGGs of the cerebellum (82% of tumors) (Hawkins et al., 2011). Other genetic mechanisms that lead to Ras/MAPK pathway activation in PLGGs—such as BRAF V600E mutations, RAS or RAF1 alterations, FGFR and NTRK2 mutations—are rare in the cerebellum (Dougherty et al., 2010; Jones et al., 2013).

DYSPLASTIC GANGLIOCYTOMA OF THE CEREBELLUM (LHERMITTE–DUCELLOS DISEASE)

Dysplastic gangliocytoma of the cerebellum is a slow-growing cerebellar mass and it is a matter of debate whether it represents a neoplasm or a hamartoma (Robinson and Cohen, 2000; Capone Mori et al., 2003). Histologically, the lesion comprised dysplastic ganglion cells localized predominantly in the internal granule cell layer (Abel et al., 2005). The imaging characteristics may be sufficient for diagnosis, due to a typical striated pattern on T2-weighted sequences with lack of contrast enhancement (Thomas et al., 2007). It is associated with Cowden syndrome, an autosomal-dominant multiple hamartoma-neoplasia syndrome caused by germline mutations in the tumor suppressor gene PTEN on chromosome 10 (Robinson and Cohen, 2000).

HEMANGIOBLASTOMA

Hemangioblastomas are benign tumors that arise in the cerebellum, brainstem, and/or spinal cord/canal, that occur sporadically (usually solitary) or associated with von Hippel–Lindau disease (often multiple lesions) (Neumann et al., 1989). Though lesions are often asymptomatic and detected on surveillance scans in patients with von Hippel–Lindau disease, some tumors may present with neurologic symptoms through compression of nearby structures, intratumoral bleeding, or paraneoplastic syndromes.

MISCELLANEOUS/RARE CEREBELLAR TUMORS

Several benign (WHO I and II) rare tumor entities with variable degrees of neuronal and/or glial components can arise in the cerebellum, including dysembryoplastic neuroepithelial tumor, ganglioglioma, gangliocytoma, desmoplastic infantile astrocytoma/ganglioglioma, and cerebellar liponeurocytoma. Similarly to low-grade gliomas, BRAF alterations are common in certain subtypes and, when treatment is indicated, surgical resection is the preferred approach.

CLINICAL PRESENTATION

Clinical presentation of cerebellar tumors is associated with tumor size, location, and patient age. Congenital CNS tumors are associated with an increased risk of perinatal complications, including fetal distress, prolonged labor, or dystocia (Fort and Rushing, 1997). In infants the clinical manifestations are variable and include irritability, vomiting, regression of developmental milestones (particularly motor skills), failure to thrive, and macrocephaly (Dobrovoljac et al., 2002). Hydrocephalus leads to progressive macrocephaly due to open fontanel and sutures and it is less likely to cause the classic symptoms of increased intracranial pressure.

Older children and teenagers with cerebellar tumors present typically with symptoms of increased intracranial pressure—headaches, nausea, vomiting, and papilledema on examination—due to hydrocephalus secondary to CSF flow obstruction. Other frequent findings include gait and truncal ataxia, dysmetria, and nystagmus.

DIAGNOSTIC WORKUP

Imaging – brain MRI

Patients with suspected brain tumor should have urgent MRI of the brain, including contrast-enhanced sequences. Postoperative MRI provides an objective assessment of residual tumor volume and has prognostic significance in MB, ependymoma, and other childhood brain tumors. Postoperative neuroimaging should be performed within 48–72 hours. Postoperative reactive enhancement is exacerbated after that and renders interpretation difficult. If the first MRI post surgery is inconclusive it should be repeated after 2–3 weeks postsurgery (Warren et al., 2018).

Imaging – spine MRI

PLGGs of the cerebellum are localized and dissemination into the leptomeningeal space is rare, so that imaging of the spine should be limited to patients with presentation suggestive of spinal disease. All other patients with cerebellar tumors should have an MRI of the spine done at diagnosis, ideally preoperatively. Baseline assessment
of spinal disease is complicated if done postoperatively due to subdural and subarachnoid blood collections.

If preoperative imaging cannot be undertaken or if inconclusive, the current recommendation is that the spine should be examined within 48–72 hours postoperatively and, in case of significant postoperative changes, repeated 2–3 weeks postsurgery. Recommendations from the Response Assessment in Pediatric Neuro-Oncology Committee define mandatory sequence acquisition standards to optimize detection of leptomeningeal metastases with clinical imaging (Warren et al., 2018).

**Lumbar puncture and CSF cytology**

Unless medically contraindicated, patients with leptomeningeal seeding tumors, including MB, AT/RT, and ependymoma, should undergo lumbar puncture for CSF cytology within 14 days post surgery. Intraoperative sampling is not recommended due to potential CSF contamination with tumor cells derived from the surgical bed.

**Other staging studies**

Metastases of childhood cerebellar tumors are predominantly leptomeningeal. Extraneural metastases, particularly bone marrow, are described in some tumors, such as MB and AT/RT, but are exceedingly rare and – unless symptoms and clinical findings suggest otherwise – no further staging tests are routinely performed. Patients with AT/RT should undergo a renal ultrasound to rule out a synchronous renal rhabdoid tumor.

**Genetic studies**

Several pediatric CNS tumors are associated with genetic syndromes and, though not yet universally implemented, it is recommended that children at higher risk be offered genetic counseling and testing to rule out germline mutations. This includes all children with SHH MB for testing of *PTCH*, *SUFU*, and *TP53* germline mutations (Ramaswamy et al., 2016b). Similarly, children with CNS AT/RTs should be investigated for germline mutations in *SMARCB1* and tumor surveillance should be discussed with affected family members.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of cerebellar mass lesions includes infection/abscess, vascular malformations, and focal demyelinating diseases. Though acute intracranial hemorrhage is more common with arterial aneurysm and arteriovenous malformations, it may also be a presenting symptom of malignant brain tumors. Imaging, in particular MRI, MR angiography, and catheter digital subtraction arteriography, is helpful to estimate time of onset, location, and relation with the vascular structures.

**TREATMENT AND OUTCOME**

Treatment of pediatric cerebellar tumors is determined by tumor biology, location, extension, metastatic status, and patient age. Below we review some of the current therapeutic strategies for the main pediatric cerebellar tumors.

**Medulloblastoma**

MBs are aggressive tumors with a propensity to disseminate and thus treatment aims at both local and systemic control of disease, using a combination of surgery, radiotherapy (for children older than 3–5 years), and chemotherapy. Until now, patients have been stratified for treatment based on three main clinical criteria: age, residual disease post surgery, and the presence of metastases. Patients with residual tumor > 1.5 cm² in postsurgical imaging and/or evidence of leptomeningeal dissemination are classified as high-risk and all others are treated as average-risk. Children under the age of 3 years are collectively considered high-risk and treated using separate radiation-sparing treatment approaches.

Based on analysis of large cohorts of MB, a number of subgroup-specific molecular markers have been proposed and should be validated in future prospective studies (Jones et al., 2012; Shih et al., 2014; Clifford et al., 2015). A recent expert consensus statement proposed recommendations for a new patient risk stratification and clinical trial design in the molecular era (Ramaswamy et al., 2016b). The first clinical trials using molecular subgrouping are ongoing but focus predominantly on WNT MB.

Surgery is generally performed shortly after diagnosis of MB. In addition to providing sufficient tissue for diagnosis, one of the main goals of surgery is to re-establish CSF flow. Preoperative management is primarily dominated by assessment and treatment of increased intracranial pressure. Patients with more severe signs, papilledema, and significant visual symptoms may require an external ventricular drain followed by immediate surgical resection. A delay between external ventricular drain placement and tumor resection increases the risk of transtentorial upward herniation.

A recent study on a large cohort of MBs challenged the prognostic role of extent of resection, taking into account subgroup affiliation. Though based on retrospective data, this study found no significant survival benefit with greater extent of resection for patients with WNT, SHH, or group 3 tumors and in patients with group 4 tumors there was an impact on progression-free survival but not on overall survival (Thompson et al., 2016). Maximum safe surgical resection remains the standard of care but removing small residual tumors offers no benefit, may carry significant neurologic complications, and is thus not recommended.
Two complication syndromes are characteristic of the postoperative period after posterior fossa tumor resection in children, seen in but not limited to patients with MB: aseptic meningitis and posterior fossa syndrome (also known as cerebellar mutism syndrome). Aseptic meningitis may occur in up to 5% of patients 5–10 days after surgery and is more common with large postoperative pseudomeningoceles (Dubey et al., 2009). The symptoms range from mild to severe and, after analysis and culture of CSF to rule out infectious causes, corticosteroids can be used with good symptom improvement.

The posterior fossa syndrome (or cerebellar mutism syndrome) was first recognized in the early 1980s (Hirsch et al., 1979; Wisoff and Epstein, 1984). This syndrome affects a significant proportion of children after posterior fossa tumor resection (11–29%) and is well documented for children with MB. Deficits in speech and language with near or complete loss of speech are characteristic (hence the name “cerebellar mutism”), and usually accompanied by lower cranial nerve, cerebellar, visual and motor abnormalities, as well as behavioral changes and emotional lability. The symptoms usually become apparent 1–4 days post surgery and are thought to be due to injury of the dentatothalamocortical pathways (Gudrunardottir et al., 2011). Though most patients recover functional speech over several weeks to months, some patients have persistent residual speech and motor impairment, and possible behavioral/affective deficits.

Postsurgical management generally consists of craniospinal irradiation (CSI) (for patients older than 3–5 years) followed by chemotherapy. The dose of CSI is adjusted according to risk group and high-risk patients receive a total of 36 Gy to the whole neuroaxis, whereas standard-risk patients receive 24 Gy, and all have an additional tumor bed boost up to 54 Gy. Though MB is radiosensitive and CSI is a cornerstone of treatment, the long-term side-effects of irradiating a developing CNS are numerous and often devastating. Given the excellent outcome of patients with WNT MB, clinical trials are currently under way in Europe and North America that evaluate de-escalation of therapy, reducing the dose of CSI further for patients with localized WNT MB.

Chemotherapy is part of all protocols used to treat children and adolescents with MB but is still a matter of debate for treatment of adult MB, for whom evidence-based treatment recommendations are lacking given the rarity of disease. MBs are responsive to a multiple of chemotherapeutic agents, including cisplatin, carboplatin, cyclophosphamide, vincristine, CCNU, etoposide, busulfan, and thiotepa. Adding chemotherapy to treatment protocols has not only led to improved survival overall but allowed the reduction of CSI dose for average-risk patients.

Maintenance chemotherapy consisting of cisplatin, lomustine, and vincristine after reduced-dose 24 Gy results in 5-year overall survival >85% (Packer et al., 2006; Lannerling et al., 2012). A strategy using high-dose cyclophosphamide-based chemotherapy followed by autologous stem cell reinfusion results in similarly favorable outcomes for average-risk patients and 5-year overall survival of 70% for high-risk patients (Gajjar et al., 2006).

Infants and children under the age of 3–5 years are treated without CSI due to the unacceptable toxicities and impact on CNS development. Several protocols explored the use of high-dose chemotherapy and autologous stem cell rescue; however, some patients received radiation at the physician’s discretion (Chi et al., 2004; Cohen et al., 2015). Overall, the prognosis of young children with metastatic MB remains dismal, with 5-year overall survival outcomes of 30%, and newer therapies are needed.

**Ependymoma**

Metastases are rare in ependymoma and upfront treatment aims at local disease control. Treatment of ependymoma consists of maximal safe resection followed by focal radiotherapy. The extent of resection is highly prognostic, as well as the presence of histologic features associated with aggressive tumor behavior, such as anaplasia (Tamburrini et al., 2009). Though gross total resection is the goal, surgery is often challenging, especially for posterior fossa ependymomas in close proximity to the brainstem. After maximum safe resection, residual tumor is left in 20–40% of the patients (Ramaswamy et al., 2016a). The use of intraoperative imaging allows assessment of degree of resection and allows the surgeon to optimize the resection if necessary.

Regardless of the degree of resection, focal radiotherapy is standard of care for children older than 3 years of age and studies have lowered the threshold to 1 year of age, with a 7-year event-free and overall survival of 69.1% and 81.0%, respectively (Merchant et al., 2009). Unless there is evidence of leptomeningeal dissemination, CSI is not recommended. Due to differences in dose distribution, proton radiotherapy may provide more sparing treatment of normal surrounding tissues when compared to the more commonly used photon radiotherapy, which is particularly relevant for treatment of young children (MacDonald and Yock, 2010).

Ependymomas are relatively chemoresistant tumors but there are ongoing trials in Europe and North America investigating the role of adjuvant chemotherapy. High-dose chemotherapy is generally not beneficial except for young children (Shih et al., 2008).

**Atypical teratoid/rhabdoid tumor**

AT/RTs were initially thought to be uniformly fatal, but there is increasing evidence showing that, despite overall
poor outcome, sustained responses can be achieved with multimodal therapy in a minority of children with AT/RT. Even with aggressive therapy, including multiagent chemotherapy, high-dose chemotherapy with stem cell rescue, and intrathecal chemotherapy combined with early involved-field irradiation, most patients survive less than 1 year after diagnosis (Tekautz et al., 2005; Finkelstein-Shechter et al., 2010).

Cerebellar pediatric low-grade gliomas

PLGGs of the cerebellum are usually large at presentation and characteristic cystic elements are common on imaging. Given that PLGGs can be cured by gross total resection alone, surgery is the mainstay of treatment and the prognosis is largely determined by extent of resection. Whereas unresectable PLGGs in deep-seated midline location often undergo multiple progressions and require several lines of therapy, cerebellar PLGGs are generally easily accessible and amenable to gross total resection. As such, cerebellar PLGGs have perhaps the best prognosis of all brain tumors, with 10-year overall survival approaching 100% (Bandopadhayay et al., 2014; Krishnatry et al., 2016). Unlike adult low-grade gliomas, PLGGs rarely undergo malignant transformation (Mistry et al., 2015).

In rare cases, residual unresectable tumors located in the cerebellum may progress and lead to clinical deterioration, requiring further therapy. Given the benign nature of these tumors, chemotherapy is the first line of treatment and radiotherapy is not recommended. The regimens more commonly used include monotherapy with vinblastine or a combination of vincristine/carboplatin (Bouffet et al., 2012).

TREATMENT-RELATED ADVERSE EVENTS

Children treated for brain tumors often face severe long-lasting sequelae, which may worsen or manifest only several years after the diagnosis. Continued long-term follow-up by a multidisciplinary team with expertise in caring for these patients is crucial.

Neurocognitive decline is a major issue for children treated with CSI. The impact on intellectual function is age- and dose-dependent and has no plateau (Moxon-Emre et al., 2014). Additional risk factors include perioperative complications, and chemotherapy, in particular methotrexate (Duffner, 2010). In all, 20–30% of adult survivors of pediatric CNS tumors have severe neurocognitive impairment, with significant impact in quality of life and association with lower educational attainment and nonindependent living (Brinkman et al., 2016).

Radiation necrosis is an important treatment complication. The onset of signs and symptoms is usually 2–3 years after radiation but reports in the literature range from 9 months to several years after radiation (Fouladi et al., 2004; Lawrence et al., 2010). Though often asymptomatic and detected on surveillance imaging, radiation necrosis may cause significant and persistent neurologic injury and, acutely, cause significant edema, requiring prolonged steroid use and/or surgery. Importantly, necrotic lesions may be misdiagnosed as tumor progression/recurrence and both entities are often difficult to differentiate by conventional MRI. Advanced functional MRI may help facilitate correct differentiation. A high index of suspicion is crucial to avoid inappropriate use of chemotherapy or other antitumor therapies.

Acute and/or chronic toxic leukoencephalopathy is a complication of treatment often associated with therapy with methotrexate and radiation therapy. There is a broad spectrum of severity and, whereas most cases are mild or asymptomatic white-matter changes on imaging, cases of severe necrotizing leukoencephalopathy and death are reported.

There is an increased risk of secondary malignancies, in particular high-grade glioma, meningioma, and acute myeloid leukemia, and the cumulative incidence continues to increase with time from treatment (Tsui et al., 2015). Endocrinopathies – growth hormone deficiency, thyroid and gonadal dysfunction – are very frequent and seen in the majority of children after CSI. Other sequelae include increased risk of sensorineural hearing loss related to radiation and ototoxic chemotherapy with cisplatin, cataracts, and stroke (King et al., 2017).

There is a spectrum of long-term cognitive and behavioral sequelae of cerebellar lesions that have been described as “cerebellar cognitive affective syndrome” (Schmahmann et al., 2007), characterized by impaired executive function and spatial cognition, speech difficulties, and behavioral and personality changes, highlighting the role of the cerebellum in nonmotor functions. Two distinct behavioral patterns have been observed, one with depression and anxiety, and the other with psychoticism and aggressive behavior, referred to by Schmahmann et al. (2007) as “dysmetria of thought.”

REFERENCES


**CEREBELLAR TUMORS**


