Brain Tumors in Children

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Preface

Brain tumor programs are like orchestras—several components all working together seamlessly to provide optimal clinical care and conduct basic, translational, and clinical research, and thus advance the field. The last decade has witnessed unprecedented advances in the field of neuro-oncology that have impacted the entire practice of treating children with brain tumors. Using modern molecular technologies that have facilitated a unique insight into the genomic make up of pediatric brain tumors, we have gained in-depth knowledge into the genetic heterogeneity of these tumors. This knowledge has also generated a new classification that is gradually being implemented by the World Health Organization (WHO). The fields of neurosurgery, neuroimaging, and radiation oncology have witnessed technological advances that have revolutionized how these modalities have been deployed in the treatment of children. The introduction of targeted therapies based on tumor molecular profiling has injected a new era of hope for curing brain tumors that were incurable in the past. Neurocognitive deficits, which are a significant concern in children treated for brain tumors, are being addressed with interventions that promise to remediate some of the damage. Long-term follow-up of brain tumor survivors has documented the unique health risk profile that these children carry for their life based on their treatment history. The recognition that more than two-thirds of the burden of pediatric cancer occurs in developing countries raises unique challenges regarding delivery of adequate therapy to this disadvantaged population. The authors of the individual chapters, all experts in their own domains, have done an outstanding job of succinctly documenting the recent advances and providing a glimpse of where the field is headed over the next few years. This book is a must-read for trainees, junior and seasoned practitioners in the field as it provides a lucid update in a rapidly emerging field.

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Nicholas A. Vitanza, Cynthia J. Campen, and Paul G. Fisher

1.1 Introduction

Tumors of the central nervous system (CNS) comprise a broad and diverse collection of neoplasms within pediatric oncology. Yet when taken together pediatric brain and spine tumors represent the most common childhood cancer with an incidence of 5.57 per 100,000 annually and are a leading cause of cancer-related death in patients under 19 years of age (Ostrom et al. 2014; Siegel et al. 2015). Factors such as genetic predisposition, age, and sex play an increasingly significant role in understanding presentation, management, and etiology of childhood brain tumors. Although long-standing observations regarding general patterns of CNS tumors continue to be clinically useful, the introduction of molecular subtypes, such as in medulloblastoma and ependymoma, and the discovery of epigenetic regulators, such as in diffuse intrinsic pontine gliomas (DIPG) and other diffuse midline gliomas with H3K27M mutations, have repurposed epidemiological findings and reconceptualized CNS tumor classification (Louis et al. 2016). The elucidation of the molecular profile of pediatric CNS tumors has made it clear that epidemiology, viewed through a prism of genetics and epigenetics, can offer even greater insights into this incredibly challenging group of tumors. Epidemiology today considers not only environmental, parental, and birth factors that may increase the risk of pediatric CNS tumors, but also germline and molecular features that are causal or pathognomonic of tumor types and subtypes.

1.2 Astrocytomas and Other Gliomas

The gliomas are a heterogeneous group of tumors, comprised mostly of astrocytomas. Pediatric astrocytomas are divided into four grades by the World Health Organization (WHO), with pilocytic astrocytomas (WHO grade I) being the most common subtype of pediatric CNS tumor, comprising approximately 15% (Ostrom et al. 2014; Louis et al. 2007). The incidence of pilocytic astrocytomas in children in England and the USA is 0.75–0.97 per 100,000, and these tumors have an exceedingly low incidence of metastasis or malignant transformation (Ostrom et al. 2014; Stokland et al. 2010; Fisher et al. 2008; Arora et al. 2009). Although they may occur in any CNS location including the spine, they most commonly arise from the posterior fossa, optic pathway and hypothalamus, or brain stem (Fernandez et al. 2003; Gajjar et al. 1997;

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Hayostek et al. 1993; Khatib et al. 1994). Diffuse astrocytomas (WHO grade II), anaplastic astrocytomas (WHO grade III), and glioblastomas (WHO grade IV) have an incidence of 0.27, 0.08, and 0.15 per 100,000 children 0–14 years of age, respectively. Low-grade gliomas, which are comprised of WHO grade I and II astrocytomas as well as WHO grade I gangliogliomas, most commonly present with greater than 6 months of symptoms (Fisher et al. 2008). The incorporation of molecular characteristics in the 2016 WHO classification of tumors of the CNS will assist in a deeper epidemiological understanding by addressing distinct biologic entities, such as diffuse gliomas with IDH mutations and diffuse midline gliomas with H3K27M mutations (Louis et al. 2016).

Children with pilocytic astrocytomas have excellent outcomes of >96% overall survival (OS) at 10 years, and patients with subtotal resections do not do significantly worse than patients with gross total resections (Ostrom et al. 2014; Gajjar et al. 1997). Posterior fossa tumors are common in children, with pilocytic astrocytomas being the second most common tumor arising in that location, behind only medulloblastoma; mean age of occurrence is 7.1 years (Smoots et al. 1998). Up to 60% of pilocytic astrocytomas are associated with a KIAA1549:BRAF fusion, which is associated with a better outcome (Becker et al. 2015; Jones et al. 2008). Optic pathway and hypothalamic astrocytomas are most often pilocytic astrocytomas, but other subtypes of low-grade gliomas also account for a small number of cases (Hoffman et al. 1993; Laithier et al. 2003). Optic pathway gliomas (OPGs) occur in approximately 15% of patients with neurofibromatosis type 1 (NF1), though they most often occur sporadically (Listernick et al. 1989). OPGs are reported to have a broad median age between 4.3 and 8.8 years, and those occurring in patients with NF1 present at a significantly earlier age than sporadic cases (Listernick et al. 1989; Nicolin et al. 2009; Singhal et al. 2002; Ahn et al. 2006; Janss et al. 1995; Khafaga et al. 2003; Jahraus and Tarbell 2006; Avery et al. 2011). The variation in age of presentation may be secondary to the presence of a cancer predisposition syndrome in NF1 patients, as well as the practice of asymptomatic surveillance imaging in that group, while 90% of sporadic cases present with new neurologic symptoms. Subependymal giant cell astrocytomas (SEGAs) are another WHO grade I astrocytoma subtype that develop almost exclusively in patients with tuberous sclerosis (TS), which occurs in 1 in 5600 live births (O'Callaghan et al. 1998). Five to twenty percent of patients with TS develop SEGAs, often in adolescence, but congenital cases have also been reported (Adriaensen et al. 2009; O'Callaghan et al. 2008; Hahn et al. 1991).

Several WHO grade II subtypes can be distinguished by histology and presentation. Pilomyxoid astrocytomas (WHO grade II) have a more aggressive course than pilocytic astrocytomas (WHO grade I), a greater propensity for growing in the hypothalamochiasmatic region, and often present earlier with a mean age of 3.3 years (Bhargava et al. 2013). Pleomorphic xanthoastrocytomas (WHO grade II) are typically located in the superficial temporal lobe; they classically present with seizures and have a median age at diagnosis of 20.5 years and an approximately 75% overall survival (Gallo et al. 2013; Perkins et al. 2012). These can rarely transform into a high-grade glioma.

Low-grade gliomas of the brain stem can be pilocytic astrocytomas or gangliogliomas, which typically occur dorsally and have the possibility of long-term cure. WHO grade II, III, and IV gliomas of the brain stem have dismal outcomes and together comprise diffuse intrinsic pontine glioma (DIPG). The 2016 WHO classification has adjusted that nomenclature in favor of diffuse midline gliomas, as diffuse gliomas of the pons, thalamus, and spinal cord may form a more biologically distinct category when H3K27M mutations are present (Louis et al. 2016; Shankar et al. 2016).

DIPGs arise most commonly in the ventral pons and comprise 10–15% of all pediatric CNS tumors and 80% of brain stem gliomas, affecting roughly 300 children in the USA each year (Ostrom et al. 2014; Ramos et al. 2013; Smith et al. 1998). Males and females are affected equally and the median age of presentation is

7 years (Lassiter et al. 1971; Lober et al. 2014; Veldhuijzen van Zanten et al. 2014). Presentation usually consists of a classic triad of ataxia, cranial nerve palsies, and pyramidal tract signs developing over 1 month, although atypical cases can present more slowly over several months (Fisher et al. 2000). It is now recognized that approximately 17% of patients undergo both local and distant neuraxis dissemination by 15 months, which is not far beyond the median overall survival of patients with DIPG, as only 10% of patients survive beyond 2 years and only 2–3% are considered long-term survivors (Gururangan et al. 2006; Hargrave et al. 2006; Jackson et al. 2013). Recently, 80% of DIPGs have been found to harbor mutations in K27M of histone 3.1 or 3.3, which are associated with mutations in *ACVR1* and *p53*, respectively (Taylor et al. 2014; Wu et al. 2012).

High-grade gliomas (HGGs) occur much more frequently in adults, with an increasing incidence with age to a peak between the ages of 75 and 85 years (Ostrom et al. 2014). The outcomes of patients with high-grade gliomas appear to be inverse to patient age, as 5-year overall survivals for children less than three and those 3–14 years of age are 31–66% and 19%, respectively (Mathew et al. 2014). Glioblastoma has been reported in classic CNS tumor predisposition syndromes, such as neurofibromatosis, Li–Fraumeni, and Turcot syndromes, as well as in several genitourinary syndromes, such as Turner and Mayer–Rokitansky–Küster–Hauser syndrome, though the majority of cases are believed to be sporadic (Hanaei et al. 2015; Jeong and Yee 2014; Macy et al. 2012; Gonzalez and Prayson 2013).

1.3 Embryonal Tumors

Embryonal brain tumors are a diverse group of aggressive neoplasms, including medulloblastoma, primary neuroectodermal tumors (PNET), atypical rhabdoid/teratoid tumors (ATRT), and pineoblastoma, which share high mitotic activity and a predilection for dissemination throughout the neuraxis, and are all WHO grade IV (Louis et al. 2007). They account for 15% of CNS tumors in patients 0–14 years of age and 12% in those 0–19 years of age, with incidences of 0.78 and 0.64 per 100,000, respectively; these incidences have remained unchanged since at least 1990 (Ostrom et al. 2014; Johnston et al. 2014). Embryonal CNS tumors rarely occur outside of childhood with the median age at presentation being 7.3 years, and 44% of them being diagnosed between the ages of 4 and 9 years (Ostrom et al. 2014; Kool et al. 2012). Medulloblastomas, the most common malignant brain tumor in pediatrics, histologically appear as PNETs specifically arising in the posterior fossa (Northcott et al. 2011). A minority of medulloblastoma cases have been reported in patients with genetic predisposition syndromes such as Gorlin, Turcot B, Li–Fraumeni, ataxia telangiectasia, Nijmegen breakage, Rubenstein–Taybi, and Coffin–Siris syndromes (Distel et al. 2003; Hart et al. 1987; Larsen et al. 2014; Skomorowski et al. 2012; Taylor et al. 2001; Rogers et al. 1988). Overall, there is a male predominance of 1.5:1, with females reported to have superior outcomes, although again this is likely subgroup dependent, as there are fewer females in the higher risk Group 3 and 4, while more young females have sonic hedgehog (SHH) driven tumors (Louis et al. 2007; Northcott et al. 2011). Historically, patients clinically classified as average-risk had a 5-year OS of roughly 85%, while high-risk patients suffered poorer outcomes with near 70% OS and patients with large-cell anaplastic histology had particularly dismal outcomes (Kool et al. 2012; Gajjar et al. 2006; Packer et al. 2006; Tarbell et al. 2013; Ramaswamy et al. 2013). Overall, long-term survival in patients with medulloblastoma is achieved in only 66% of patients, with 10% suffering from secondary malignancies, 32% of which are secondary brain tumors (Ning et al. 2015).

Although particular subsets of medulloblastoma have long been suspected to behave differently, it is now commonly accepted that there are four distinct molecular subgroups: WNT, SHH, Group 3, and Group 4, which account for 11%, 28%, 27%, and 34% of cases, respectively (Kool et al. 2012; Northcott et al. 2011; Badiali et al. 1991).

Prodromes may vary among the groups, ranging from only 2 weeks in patients with SHH tumors, to 4 weeks in patients with Group 3 tumors and 8 weeks in patients with WNT or Group 4 tumors (Ramaswamy et al. 2014). Furthermore, age of presentation varies as the incidence of SHH medulloblastomas is bimodal, peaking under 3 years and again over 15 years of age (Northcott et al. 2011). WNT and Group 4 both peak around age 11, but WNT tumors are essentially absent in infancy (Kool et al. 2012; Northcott et al. 2011). WNT tumors have no gender predominance, are the least frequent subgroup, and experience the best outcomes with greater than 90% overall survival (Ellison et al. 2011, 2011). Outcomes in patients with SHH tumors are inferior, though strongly age-dependent as the 10-year OS is 77% and 51% in infants and children, respectively (Kool et al. 2012; Ramaswamy et al. 2013). Despite presenting with metastatic disease in 17% of infants and 22% of children, SHH tumors most often recur locally (Kool et al. 2012; Ramaswamy et al. 2013). Group 3 and Group 4 occur nearly twice as often in males, accounting for the male predominance in medulloblastoma as a whole. Forty-seven percent of Group 3 medulloblastomas present with metastases and, while they do not have significantly worse prognoses than those without metastases, this subgroup overall suffers the poorest outcomes with long-term survival in less than 50% of patients (Kool et al. 2012; Northcott et al. 2011). Group 4 patients, on the other hand, have significantly different outcomes associated with the presence of metastases, ranging from nearly 40% OS (metastases present) to greater than 70% (metastases absent) (Kool et al. 2012). In patients that experience recurrence, the molecular subgroup remains consistent, and although outcomes are uniformly poor, Group 4 patients have the longest survival following recurrence (Ramaswamy et al. 2013).

Atypical teratoid/rhabdoid tumors (ATRTs) are embryonal CNS tumors with rhabdoid features that were initially described in the 1990s (Zuccoli et al. 1999). Since their initial description their incidence has increased, while the incidence of other PNETs has declined, more likely representative of a change in classification than a change in biological patterns of disease (Ostrom et al. 2014). The incidence of ATRT in childhood is approximately 0.1 per 100,000 with a peak between 1 and 2 years of age and no gender predisposition observed in the USA (Ostrom et al. 2014, b; Hilden et al. 2004; von Hoff et al. 2011; Woehrer et al. 2010). They account for 10% of CNS tumors in patients less than 1 year of age, but only 1.6% of all childhood brain tumors (Ostrom et al. 2014). The wide range of reported OS, between 28 and 48%, may be affected by delays in appropriate diagnosis, as one report noted a 5-year OS of only 15% in patients who were initially misdiagnosed (Ostrom et al. 2014; Hilden et al. 2004; von Hoff et al. 2011; Woehrer et al. 2010; Athale et al. 2009; Lafay-Cousin et al. 2012). Most reports conclude that metastatic disease at presentation is not prognostic, while descriptions of the prognostic impact of age differ (Ostrom et al. 2014; Hilden et al. 2004; von Hoff et al. 2011; Woehrer et al. 2010; Athale et al. 2009; Lafay-Cousin et al. 2012). The location of ATRTs, however, does appear to change with age, as patients under 1 year of age most commonly have infratentorial disease and the incidence of supratentorial disease increases with age (Ostrom et al. 2014). The characteristic loss of *INI1* in these tumors is most commonly somatic, although germline mutations have been reported and can result in a rhabdoid tumor predisposition syndrome (RTPS) (Sredni and Tomita 2015; Taylor et al. 2000). The development of ATRTs has also been associated with low birth weight and twin pregnancies (Heck et al. 2013).

Pineoblastomas are malignant tumors of the pineal gland that, like other PNETs, are histologically similar to medulloblastomas, but display a distinct biology (Li et al. 2005). While some pineal tumors, such as germ cell tumors, occur more commonly in males, reports suggest pineoblastoma may be more common in females (Villa et al. 2012; Fauchon et al. 2000). Although patients with bilateral retinoblastomas may develop a pineoblastoma, "trilateral retinoblastoma" occurs in only 1% of patients with bilateral retinoblastoma and only in the setting of germline mutations (Ramasubramanian et al. 2013). While the majority of pineoblastoma cases appear sporadic, cases also have been reported as

part of Turcot syndrome and with germline *DICER1* mutations (Ikeda et al. 1998; Gadish et al. 2005; Sabbaghian et al. 2012).

1.4 Ependymoma

Virchow initially described ependymomas in the nineteenth century as CNS tumors originating from the walls of the ventricular system (Virchow 1863–67). Though ependymomas likely consist of several discrete subgroups that can be distinguished by location and molecular profile, most reports evaluate ependymomas as a whole or by grade, leaving their epidemiologic understanding incomplete. Ependymoma incidence in the USA is 0.3 and 0.29 per 100,000 children aged 0–14 years and 0–19 years, respectively, and has not increased since 1973; nearly one-third of cases occur in children under the age of 4 years (Ostrom et al. 2014; McGuire et al. 2009). Although 46% of ependymomas in adults are spinal, location varies according to age in children (Vera-Bolanos et al. 2015). The mean age for spinal, supratentorial, and infratentorial ependymomas are 12.2, 7.8, and 5 years, respectively (McGuire et al. 2009). The gender incidence may be affected by age and location, as the overall male-to-female ratio is 1.3:1, though males are more commonly affected by supratentorial ependymomas (1.4:1) and less commonly affected by spinal ependymoma (0.7:1) than females (McGuire et al. 2009; Dohrmann and Farwell 1976). Presentation with metastatic disease is rare in pediatric ependymomas but is more common in infants, although reports vary on whether supratentorial or infratentorial tumors are more likely to metastasize (Zacharoulis et al. 2008; Allen et al. 1998).

Currently, the treatment of ependymoma primarily varies according to age, grade, and location. In 2015, a new molecular classification was proposed though it has yet to be validated. It divides ependymomas into anatomical compartments: supratentorial (ST), posterior fossa (PF), and spinal (SP); tumors in each compartment are then divided into one of three subgroups: a subependymoma group and two other genetic or epigenetic subgroups (Pajtler et al. 2015). Supratentorial ependymomas are distinguished by either *RELA* fusions (ST-EPN-RELA), which occur at a median age of 8 years and result in frequent disease progressions, or *YAP1* fusions (ST-EPN-YAP1), which occur at a median age of 1.4 years (Pajtler et al. 2015). Posterior fossa ependymomas are subdivided into those with a CpG methylator phenotype (PF-EPN-A), which account for 48% of all pediatric ependymomas and experience poor outcomes, and those that are not hypermethylated (PF-EPN-B), which often occur in older patients (EPN-PFB) (Pajtler et al. 2015; Parker et al. 2014; Witt et al. 2011).

Although histologic classification of WHO grade II or III in pediatric ependymoma may not offer prognostic significance, several WHO grade I subsets are clearly less aggressive neoplasms (Perilongo et al. 1997; Ross and Rubinstein 1989; Robertson et al. 1998). Subependymomas represent less than 1% of CNS tumors in children, are designated WHO grade I, and have essentially no metastatic potential (Scheinker 1945; Ragel et al. 2006). Myxopapillary ependymomas, also WHO grade I, have a median age of presentation of 36 years, yet are not uncommon in children with reports of patients as young as 6 years old being affected (Barton et al. 2010; Woesler et al. 1998). Despite their WHO grade I designation, the pediatric variant may be more aggressive than that seen in adults with a suggestion of dissemination in as many as 58% of patients (Fassett et al. 2005). Neurofibromatosis type II (NF2) is the most common hereditary predisposition for ependymoma, most often causing intramedullary spinal tumors of the cervical spine (Bianchi et al. 1994; Plotkin et al. 2011). Pediatric ependymomas have also been reported in Turcot B, MEN1, and Li–Fraumeni syndromes (Chan et al. 1999; Metzger et al. 1991).

1.5 Germ Cell Tumors

Germ cell tumors (GCTs) are a heterogeneous group of cancers with variable classification and nomenclature depending on the particular organ involvement. In the CNS, they are divided into germinomas, non-germinomatous germ cell

tumors (NGGCT), and teratomas. The most common locations for GCTs are the suprasellar and pineal regions. GCTs account for 4% of pediatric CNS tumors with an incidence of 0.2 and 0.22 per 100,000 in children aged 0–14 and 0–19 years, respectively (Ostrom et al. 2014). Males account for 76% of all CNS GCTs, 58% of pituitary GCTs, and a remarkable 93% of pineal GCTs (Goodwin et al. 2009). In both sexes there is a small spike at birth and a much greater spike in adolescence with incidences peaking at roughly age 15. Race also influences incidence patterns, as in the USA nearly 20% of patients were Asian or Pacific Islander with an incidence of 0.26 per 100,000, double the 0.13 per 100,000 in white children 0–15 years of age (Goodwin et al. 2009). CNS GCTs also account for a greater percentage of pediatric CNS tumors in Japan, Korea, Taiwan, and China at 7.8%, 11.2%, 14%, and 7.9%, respectively (Cho et al. 2002; Mori and Kurisaka 1986; Wong et al. 2005; Zhou et al. 2008). Klinefelter syndrome is associated with the development of pediatric germ cell tumors including intracranial germinomas (Arens et al. 1988). Down syndrome and NF1 have also been reported in patients with intracranial germinomas (Hashimoto et al. 1995; Wong et al. 1995).

1.6 Family History

Despite the increasing awareness of CNS tumor genetic predispositions, further discussed within another chapter, there is still little evidence of the development of CNS tumors in the parents or siblings of affected children. The studies reporting increased pediatric CNS tumor incidence among siblings have been plagued by small numbers and an inability to exclude genetic predisposition syndromes; however, a larger Nordic cohort of patients showed no association among siblings outside of genetic predisposition syndromes (Draper et al. 1977; Farwell and Flannery 1984; Miller 1971; Winther et al. 2001). There have been several reports regarding the association of parental age with pediatric CNS tumors: two studies identified increased parental age as a risk factor, while one found only advanced maternal age to be a significant risk (Hemminki et al. 1999; Johnson et al. 2009; Yip et al. 2006). A review of Sweden's Family-Cancer Database, consisting of over 13,000 CNS tumor diagnoses, found that oldest siblings were at increased risk for several childhood malignancies and this risk increased with the number of younger siblings (Altieri et al. 2006). The existence of three or more younger siblings resulted in a relative risk of 1.34, 2.3, 2.61, and 3.71 of astrocytoma, medulloblastoma, ependymoma, and meningioma, respectively (Altieri et al. 2006).

1.7 Birth History

As early as 1968, Kobayashi had published a report of the association between congenital anomalies and childhood cancer (Kobayashi et al. 1968). A review of 90,400 children found patients with congenital anomalies had a risk ratio of 5.8 (CI 3.7–9.1) of developing cancer in their first year of life (Agha et al. 2005). The risk was also increased for central nervous system and sympathetic nervous system tumors individually at a risk ratio of 2.5 (CI 1.8–3.4) and 2.2 (CI 1.4–3.4), respectively. A Bjørge et al. study of 5.2 million children and their families in Norway and Sweden also found patients with congenital anomalies had an increased cancer risk that extended into early adulthood (Bjorge et al. 2008). Furthermore, patients with CNS malformations were also at the highest risk of developing CNS malignancies, with a standardized incidence rate (SIR) of 58 (CI 41–80) and 8.3 (Louis et al. 2007; Stokland et al. 2010; Fisher et al. 2008; Arora et al. 2009; Fernandez et al. 2003; Gajjar et al. 1997; Hayostek et al. 1993; Khatib et al. 1994; Smoots et al. 1998; Becker et al. 2015; Jones et al. 2008; Hoffman et al. 1993) in Norway and Sweden, respectively. To assess potential cancer risk associated with congenital anomalies even outside of the setting of chromosomal defects, a review of the California Cancer Registry (CCR) found that between 1988 and 2004, children with congenital anomalies without chromosomal defects had a 1.8-fold increased risk of CNS cancer (Fisher et al. 2012).

A further examination found a particularly increased risk in medulloblastoma (OR 1.7, CI 1.1–2.6), PNET (OR 3.64, CI 1.5–8.6), and germ cell tumors (OR 6.4, CI 2.1–19.6), as well as an increased risk in mothers with greater than two fetal losses after 20 weeks of gestation (OR 3.13, CI 1.3–7.4) (Partap et al. 2011).

Many large studies have evaluated the impact of birth weight on the risk of developing CNS tumors, with several suggesting an increased birth weight carries a greater relative risk, although the most common specific tumors types varied among studies (Bjorge et al. 2013; Harder et al. 2008; MacLean et al. 2010; Milne et al. 2008; Schmidt et al. 2010). In an examination matching each case (17,698) to 10 controls, Bjørge found an increased childhood cancer risk for higher birth weight infants, and also infants with larger head circumferences (Bjorge et al. 2013). Additionally, in an evaluation of Nordic children, Schmidt found a gestational age-adjusted birth weight of greater than 4.5 kg increased the risk of all CNS tumors (OR 1.27, CI 1.03–1.6), with the greatest increase among embryonal tumors (Schmidt et al. 2010). When 3733 CNS tumors from the CCR were matched to controls, Maclean et al. found an increased birth weight of 4 kg associated with an increased risk of CNS tumors, especially HGGs (MacLean et al. 2010). A meta-analysis of eight studies found that increased birth weight was associated with increased incidence of astrocytomas and medulloblastomas, but not ependymomas (Harder et al. 2008). Conversely, a study of over 600,000 live births in Western Australia between 1980 and 2004 found no association between birth size and the development of CNS tumors prior to age 14 (Milne et al. 2008).

1.8 Immune System

Although allergic conditions have been consistently reported as inversely associated with adult gliomas, reports in children have varied (Chen et al. 2011). In pediatrics, an initial report from the United Kingdom found that maternal asthma resulted in a decreased relative risk of their children developing a CNS tumor, particularly PNETs (Harding et al. 2008). Another study evaluating 272 matched case–control pairs in Canada found asthma associated inversely with the development of CNS tumors, especially ependymomas, while the relationship with eczema was not significant (Roncarolo and Infante-Rivard 2012). Furthermore, the use of asthma controller medications was found to be associated with an increased risk. However, a study of 352 pediatric brain tumors in Denmark, Norway, Sweden, and Switzerland found no association with asthma or eczema (Shu et al. 2014).

Studies evaluating the influence of prior infectious history on the development of pediatric CNS tumors have been conflicting. Harding et al. found infants without social interaction with other infants in the first year of life had an increased risk (OR 1.37, CI 1.08–1.75) of CNS tumors, especially PNET, compared to those who had such interaction (Harding et al. 2009). Attendance in day care also appeared to show a protective benefit, though not statistically significant. A Canadian study also found a reduced risk in patients with day care attendance, and, unlike Harding's study, breastfeeding was found to be protective against the development of brain tumors (Shaw et al. 2006; Harding et al. 2007). Conversely, Anderson et al. found no association with day care attendance but that patients with more frequent sick days in the first 6 years of life had an increased incidence of gliomas and embryonal tumors (Andersen et al. 2013).

1.9 Environmental Exposure

Radiation therapy (RT), used decades ago to treat tinea capitis and more recently to treat childhood acute lymphoblastic leukemia (ALL), is known to cause secondary CNS tumors, especially meningiomas, *p53* mutated glioblastomas, and PNETs (Kleinerman 2006; Ohgaki and Kleihues 2005). Fifty-three percent of secondary neoplasms in survivors of childhood ALL occur in the CNS and 89% of those are associated with prior cranial irradiation (Mody et al. 2008; Schmiegelow et al. 2013). The timing and outcome are dependent

on pathology, as non-meningioma CNS tumors occur between 6.5 and 9.8 years and meningiomas occurred between 12.3 and 18.3 years after treatment, with OS of 18% and 96%, respectively (Schmiegelow et al. 2013). Prenatal diagnostic imaging has been evaluated as a potential cancer risk, but studies from the United Kingdom, Sweden, and Denmark did not describe a significant increase in pediatric CNS tumors in patients exposed to prenatal X-rays compared to controls (Mellemkjaer et al. 2006; Rajaraman et al. 2011; Stalberg et al. 2007). Diagnostic head X-rays also have not been associated with the development of CNS tumors (Khan et al. 2010). However, CT scans contribute to a slightly elevated risk of CNS tumors, with risk decreasing with increasing age at first CT scan exposure (Pearce et al. 2012; Mathews et al. 2013).

Magnetic fields, radio waves, and mobile phone use have not been found to be associated with an increase in pediatric brain tumors (Aydin et al. 2011; Elliott et al. 2010; Ha et al. 2007; Kheifets et al. 2010).

Although many different maternal medications have been evaluated, none have been found to consistently increase the risk of pediatric CNS tumors in offspring. A German study found an association between maternal prenatal antibiotic use and an increased risk of medulloblastoma (OR 2.07, CI 1.03–4.17) and astrocytoma (OR 2.26, CI 1.09–4.69) (Kaatsch et al. 2010). Although the odds ratio was similarly elevated in a Canadian study, the results were not statistically significant (OR 1.7, CI 0.8–3.6) (Shaw et al. 2006). A 2010 Swedish study evaluating potential associations with prenatal medications and the development of pediatric CNS tumors in children 0–14 years of age found no association with antibiotics, antifungals, antacids, analgesics, antiasthmatics, antiemetics, antihistamines, diuretics, folic acid, iron, laxatives, or vitamins, but did find an association with antihypertensives (OR 2.7, CI 1.1–6.5), particularly β-blockers (OR 5.3, CI 1.2–24.8) (Stalberg et al. 2010). An association between prenatal antihypertensive use and the development of pediatric CNS tumors, however, was not found in a German study evaluating pediatric CNS tumors diagnosed between 1992 and 1997 (Schuz et al. 2007). Amide or amine-containing medications can potentially be carcinogenic after conversion to N-nitroso compounds (NOCs) in the stomach, though three studies have all found little or no support for an association between maternal exposure and central nervous system tumors in subsequent children (Cardy et al. 2006; Carozza et al. 1995).

Prenatal vitamins, especially iron and folic acid, consistently have been shown to decrease the risk of pediatric CNS tumors (Bunin et al. 2005, 2006; Ortega-Garcia et al. 2010; Milne et al. 2012).

Although prenatal alcohol exposure can have a variety of toxic effects on the developing child, there is no clear increased risk of pediatric CNS tumors (Infante-Rivard and El-Zein 2007; Milne et al. 2013). The role of maternal tobacco smoking during pregnancy is unclear, as several reports have found no association (Filippini et al. 2002; Huncharek et al. 2002; Norman et al. 1996), while a review of the Swedish Birth Register of births between 1983 and 1997 found a hazard ratio of 1.24 (CI 1.01–1.53) (Brooks et al. 2004).

Pesticide exposure may have an association with pediatric CNS tumors. A review of 4723 patients from the North of England found no significant relationship between occupational exposure to pesticides and risk of any childhood cancer (Pearce et al. 2006). In contrast, a study from the USA found that paternal pesticide exposure was associated with an increased risk of his child developing an astrocytoma (OR 1.8, CI 1.1–31), but not PNET (Shim et al. 2009). A separate study investigating paternal hobbies did identify exposure to pesticides as increasing the risk of medulloblastoma and PNET (Rosso et al. 2008). An Australian study also found preconception exposure to pesticides increased the risk of pediatric CNS tumors (Greenop et al. 2013). The effect of residential pesticides may be contingent on particular predispositions as polymorphisms in *PON1*, a gene responsible for organophosphorous metabolism, may increase the risk of pediatric CNS tumors in exposed patients (Searles Nielsen et al. 2010).

An investigation of the risk of pediatric CNS tumors among children of parents working in a

wide variety of occupations found no clear associations (Mazumdar et al. 2008). However, a separate analysis found that brain tumors were more common in children of mothers working in electronic component manufacturing (OR 13.78, CI 1.45–129) and garment and textile workers (IR 7.25, CI 1.42–37) (Ali et al. 2004). There also appears to be an increased incidence of CNS tumors among children whose parents are exposed to diesel fuel, but not other exhausts (Peters et al. 2013). Paternal polycyclic aromatic hydrocarbon exposure has also been linked to a subsequent increase in pediatric CNS tumors (OR 1.4, CI 1.1–1.7) (Cordier et al. 2004).

In conclusion, pediatric neuro-oncology is a rapidly evolving field in which molecular investigations are fueling a restructuring of tumor subgroups. Although pediatric CNS tumors have historically been distinguished by histopathology and location, driving mutations and epigenetic profiles are proving to not only be attractive therapeutic targets but also epicenters for new classifications. The challenge will be to integrate former classification systems with the latter, and, perhaps just as importantly, to frame our historical data according to the new groupings so that the decades of lessons learned in epidemiology can continue to be applied in the pursuit of improving outcomes for children with CNS tumors.

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Principles of Pediatric Neurosurgery

2

P. Ryan Lingo, Asim F. Choudhri, and Paul Klimo Jr

2.1 Introduction

The incidence of primary malignant and nonmalignant central nervous system (CNS) tumors in children and adolescents aged 0–19 years in the US is 5.42 per 100,000, and approximately 4620 new cases are expected to be diagnosed in the US in 2015 (Ostrom et al. 2014). There is a rich variety of brain tumors found in children which is primarily a function of the patient's age and location of origin, with the overall most common being pilocytic astrocytoma (Ostrom et al. 2014). It has been traditionally taught that approximately 60% of pediatric brain tumors are infratentorial, but the actual ratio of supratentorial to infratentorial pediatric tumors is dependent on the specific age group (Ostrom et al. 2015). Tumors can be broadly categorized as glial (e.g., astrocytomas, ependymomas), embryonal (e.g., medulloblastomas, pineoblastoma), germ cell (e.g., germinoma, teratoma), and other (e.g., choroid plexus tumors, craniopharyngiomas).

Neurosurgery represents one of the main pillars of pediatric neurooncologic care, along with medical and radiation oncology, pathology, and neuroradiology. Neurosurgical interventions include management of hydrocephalus, obtaining tissue for histopathological and molecular diagnosis, and tumor resection for oncologic (i.e., survival) and/or neurologic (e.g. seizure control) benefit. In this chapter, we will take the reader through the surgical management of pediatric neurooncologic patients from the preoperative, intraoperative, and postoperative phases of care.

2.2 Initial Evaluation

2.2.1 History and Examination

Clinical presentation is variable and dependent on the location of the tumor and the age of the patient. Most children will present with hydrocephalus, symptoms of raised intracranial pressure, focal neurologic deficit, or a seizure. Some tumors will be incidentally found as part of a workup for nonspecific symptoms, such as headaches or after a minor traumatic event. A detailed neurological exam should be performed on all patients; a thorough knowledge of neuroanatomy can help qualitatively detail preoperative deficits, both minor and major. This is easier in older children, but

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there are specific signs and symptoms that can be revealing in younger children.

Headache is a common symptom among patients with brain tumors and occurs with, or without, elevated intracranial pressure (ICP). These headaches are classically described as being worse in the morning and exacerbated by straining, coughing, or placing the head in a dependent location. Brain tumor headaches are frequently associated with nausea and may be temporarily relieved by the hyperventilation that occurs with vomiting. In a large study examining the epidemiology of headaches associated with pediatric brain tumors, approximately two-thirds of patients had chronic or frequent headaches prior to their first admission (The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. The Childhood Brain Tumor Consortium 1991). In this study, headaches tended to be triggered by straining, coughing, or sneezing, to gradually worsen over time, to cause vomiting followed by relief, and to be severe enough to wake the child from sleep. Personality changes, school problems, and focal neurologic deficits were also associated with headaches. In a similar study, the most common symptom at presentation in children with brain tumors was headache; all of the patients with headaches also had other symptoms, including mental status changes, papilledema, eye movement derangements, hemimotor or sensory abnormalities, tandem gait difficulty, or abnormal deep tendon reflexes, present at the time of diagnosis (Wilne et al. 2006).

The two cranial nerves that can be affected by hydrocephalus or elevated ICP are the trochlear (4th) and abducens (6th). The trochlear nerve innervates the superior oblique muscle, which intorts, depresses, and adducts the eye. Patients with acquired weakness of the 4th nerve report vertical and oblique diplopia that is worse in down-gaze and gaze away from the affected eye, resulting in difficulty reading. Patients will adopt a characteristic head tilt away from their affected eye to reduce their diplopia, which is called the Bielschowsky's sign. The abducens nerve innervates the lateral rectus, which abducts the eye. Weakness of the 6th cranial nerve results in a lateral gaze palsy and horizontal diplopia that is worse with gaze toward the affected eye.

Posterior fossa tumors often present with symptoms of obstructive hydrocephalus, which in turn leads to elevated intracranial pressure. Headache and vomiting are hallmark features, particularly if present in the morning. In infants, hydrocephalus presents with a full or bulging fontanelle, separation of sutures, rapid head growth, macrocephaly, irritability, lethargy, or poor feeding/failure to thrive. Sundowning—or setting sun sign—describes downward deviation of both eyes, revealing an area of sclera above the irises. This usually occurs with advanced hydrocephalus with stretching of the third ventricle and upper brainstem. The pupils are sluggish and respond to light unequally.

Pineal region tumors can result in hydrocephalus and Parinaud's syndrome. Parinaud's syndrome, or dorsal midbrain syndrome, is a constellation of eye findings that includes upgaze palsy, convergence-retraction nystagmus, light-near pupillary dissociation (Argyll Robertson pupil), and lid retraction called Collier's sign (Baloh et al. 1985). When upgaze palsy is combined with lid retraction, it produces the setting sun sign. This syndrome is often seen with pineal region tumors that place pressure on the rostral interstitial nucleus of the medial longitudinal fasciculus and the posterior commissure, which mediate upgaze and the consensual pupillary light reflex, respectively.

Diencephalic syndrome, also known as Russell's syndrome, is characterized by progressive and severe failure to thrive (Zafeiriou et al. 2001). It is seen exclusively with suprasellar pilocytic astrocytoma tumors affecting the anterior hypothalamus. The child often appears emaciated despite being alert and active and has a "pseudohydrocephalic" face from severe loss of adipose tissue and a normal head circumference. Neurocutaneous syndromes—such as the neurofibromatoses, tuberous sclerosis, and Von Hippel-Lindau disease—are characterized by specific nervous system tumors associated with clinical exam findings. The details of these syndromes are beyond the scope of this chapter.

2.2.2 Seizures

Supratentorial tumor location, age < 2 years, and hyponatremia are independent risk factors for a first-time seizure in pediatric patients with a brain tumor (Hardesty et al. 2011). Seizures cause cerebral hyperemia and can thus precipitate a herniation event in the setting of preexisting increased intracranial pressure. They can also be the clinical manifestation of an intratumoral hemorrhage. If the patient is in status epilepticus, secondary brain damage may also occur through tissue hypoxia or acidosis. Guidelines are available that detail when imaging should be conducted in a child with a first-time nonfebrile seizure (Hirtz et al. 2000).

Antiepileptic drugs (AED)—such as phenytoin, phenobarbital, and carbamazeipine—induce the cytochrome P450 system and can reduce the efficacy of many common chemotherapeutics (Guerrini et al. 2013). Conversely, valproic acid inhibits the cytochrome P450 system and can increase levels of chemotherapeutics. Levetiracetam is a newer AED that has proven efficacious in preventing tumoral seizures with a low side-effect profile and no significant induction of the cytochrome P450 system (Zachenhofer et al. 2011). It is the first-line AED at our institution for children who suffer from seizures caused by a brain tumor.

2.2.3 Cerebral Edema

Brain tumors can cause vasogenic (i.e., interstitial) edema, which results from breakdown of the tight junctions between brain capillary endothelial cells and leakage of plasma filtrate into the interstitial space. Vasogenic edema is more marked in the white matter than the gray matter. Children are often started on steroids (e.g., dexamethasone) shortly after being diagnosed with a brain tumor. Steroids help with vasogenic edema, hydrocephalus (headaches, nausea/vomiting), and poor appetite, all of which cause the child to feel and look significantly better.

2.2.4 Preparation for Tumor Resection: Management of Hydrocephalus

For the vast majority of children, treatment of hydrocephalus is done by resecting the tumor. Prophylactic endoscopic third ventriculostomy (ETV) at the time of surgery has been shown to reduce the risk of post-resection hydrocephalus from approximately 27 to 6% in patients with posterior fossa tumors and hydrocephalus (Sainte-Rose et al. 2001). However, since resection alone effectively treats the majority of patients with posterior fossa tumor-induced hydrocephalus, pre-resection ETV is an unnecessary surgery, if tumor resection is to be carried out in a timely manner. However, if the patient's hydrocephalus will not resolve with resection (e.g., CSF dissemination), or there is no immediate role for resection (e.g., pineal mass), or no resection at all (e.g., diffuse pontine glioma), then long-term hydrocephalus management can be achieved either by placing a ventricular shunt or by performing an ETV. The ETV Success Score was developed to help surgeons determine the likelihood of ETV succeeding in a particular child, taking into consideration age, hydrocephalus etiology, and whether the child currently has a shunt or not.

Patients who present in extremis from severe hydrocephalus may require emergent placement of an external ventricular drain (EVD) (Lin and Riva-Cambrin 2015; El-Gaidi et al. 2015). Care must be taken not to drain too much cerebrospinal fluid in patients with posterior fossa tumors as this can precipitate upward transtentorial herniation (Osborn et al. 1978). Ascending transtentorial herniation results in a clinical syndrome of nausea and vomiting, followed by progression to stupor and coma with small nonreactive pupils and loss of vertical gaze. Radiographically, there is displacement of the midbrain and cerebellum through the tentorial notch, causing flattening of the quadrigeminal cistern and a "spinning top" appearance to the midbrain from compression of the posterior aspect of the midbrain.

2.2.5 Preparation for Tumor Resection: Neuroimaging

Computed tomography (CT) scans are very useful in the initial evaluation because they are quick and sensitive for detecting hydrocephalus, hemorrhage, edema, and ectopic calcifications. Once the child is deemed stable, he or she should have a magnetic resonance image (MRI) of the brain both with and without contrast. Unless the index of suspicion is low, an MRI of the full spine (with and without contrast) should also be obtained to look for leptomeningeal—or "drop"—metastases. Standard MRI brain sequences include T1 (with and without contrast), T2, FLAIR, diffusion weighted imaging (DWI) with the apparent diffusion coefficient map (ADC), and susceptibility weighted imaging (SWI). ADC maps have been shown to correlate with tumor cellularity in pediatric brain tumors (Choudhri et al. 2015a). Sometimes brain tumors can resemble other pathologies, such as infection or demyelinating disease. Magnetic resonance (MR) perfusion and spectroscopy can help distinguish tumors from other such conditions by highlighting increased blood flow and products of cell turnover, like elevated choline and depressed N-acetylaspartate, respectively.

Vascular imaging studies, such as MR or CT angiogram/venogram, are useful if tumors involve major intracranial arteries, veins, or sinovenous structures. Traditional angiography is also a valuable preoperative tool when tumors are felt to be hypervascular and may benefit from preoperative embolization (Fig. 2.1). If such

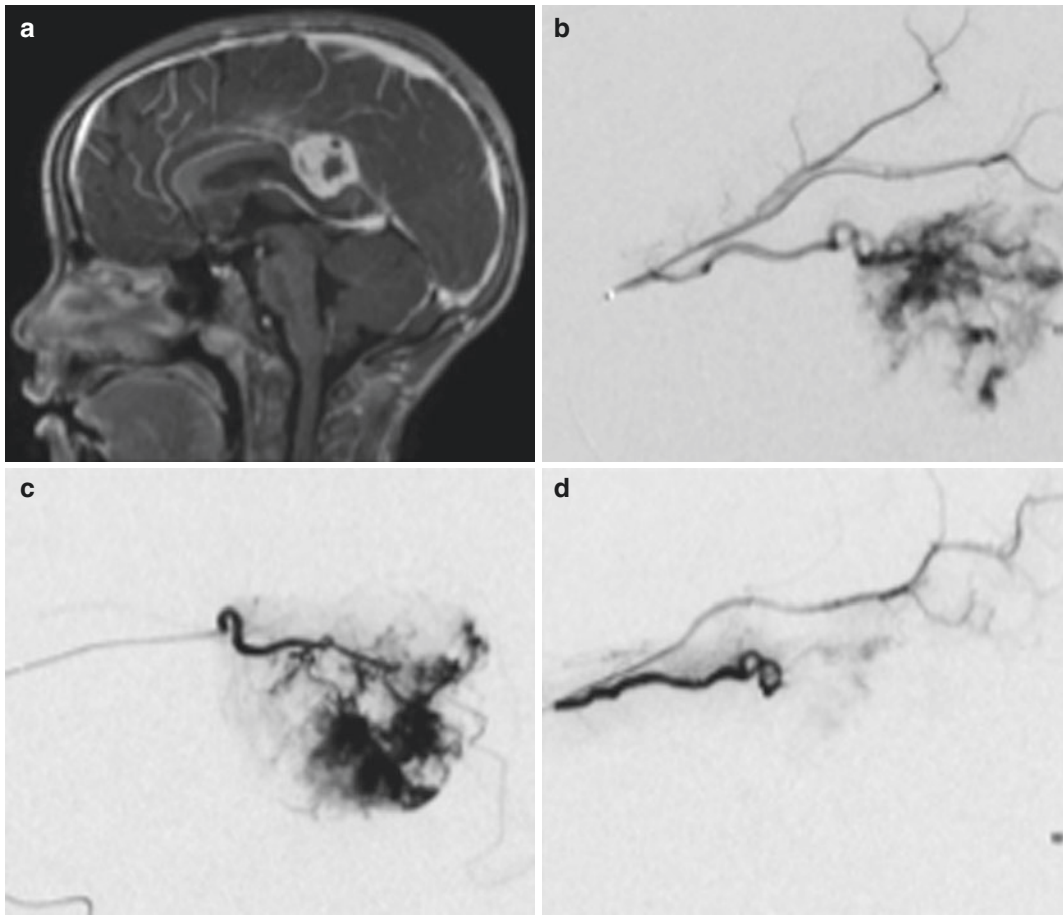

Fig. 2.1 T1 weighted (T1W) MRI with contrast of an interhemispheric hemangioma (**a**). Angiogram demonstrates vascular supply through the pericallosal artery (**b**). Microcatheterization of the tumor for embolization (**c**). Post embolization angiogram (**d**)

embolization is performed, resection should follow within 24–48 h as the embolization may cause new or worsening cerebral edema.

Eloquent location of a tumor is particularly challenging for the surgeon. Functional MRI (fMRI), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and diffusion tensor imaging (DTI) are modalities that provide further knowledge of the patient's functional neuroanatomy (Ottenhausen et al. 2015). These imaging studies may localize eloquent regions, such as the primary motor cortex, Broca's and Wernicke's area, or subcortical tracts like the corticospinal, geniculocalcarine, or arcuate fasciculus. Functional MRI relies on the theory of neurovascular coupling and assumes that when functional networks within the brain are activated, perfusion-induced changes occur regionally in the blood oxygen-level that can be detected by MRI. In young children, motor mapping can be performed with passive movement (Fig. 2.2) (Choudhri et al. 2015c). MEG detects

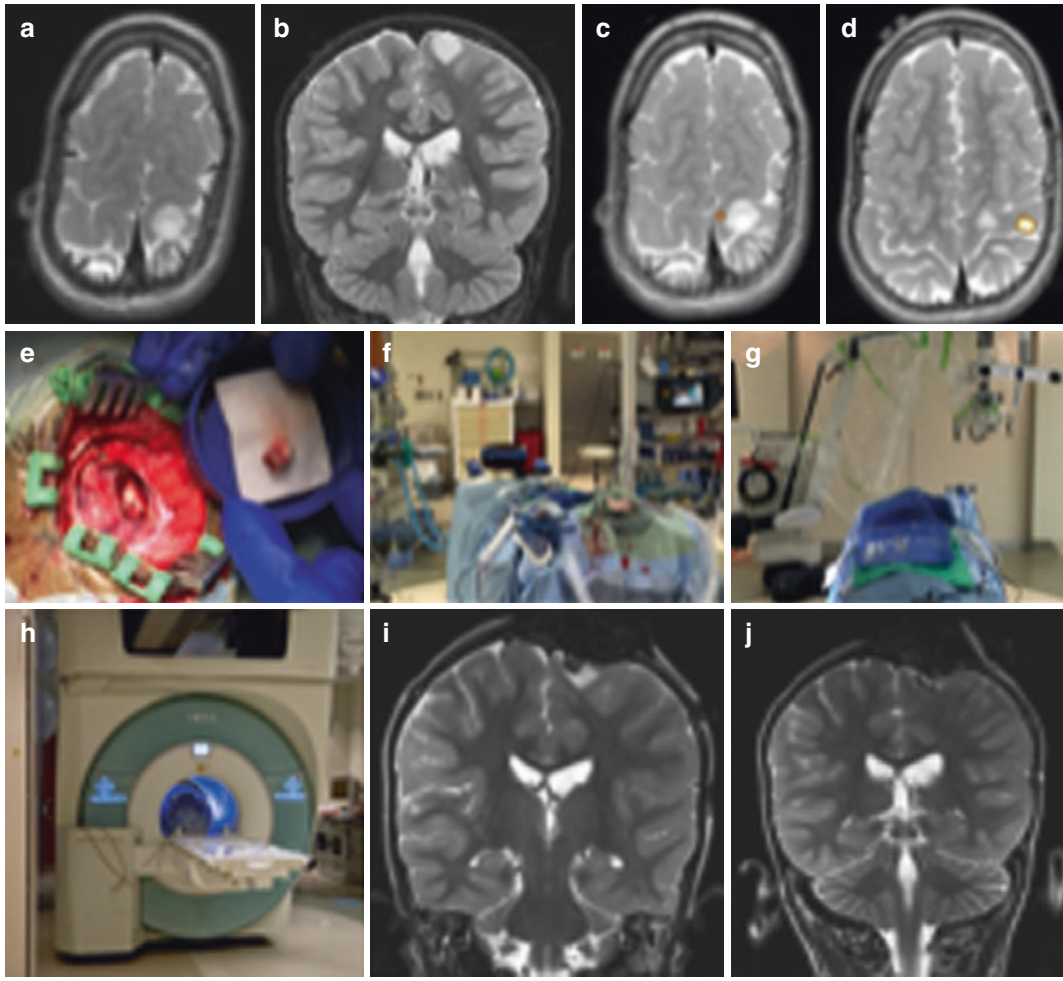

Fig. 2.2 Axial and coronal T2 weighted (T2W) MRI shows a low-grade glioma within the left precentral gyrus (**a**, **b**). Axial T2W image with functional MRI (fMRI) overlay from passive movement of the right lower extremity shows cortical activation along the medial margin of the tumor within the precentral gyrus near the vertex (**c**). Axial T2W image with fMRI overlay from passive movement of the right upper extremity shows cortical activation in the precentral gyrus inferolateral to the tumor (**d**). Resected tumor specimen (**e**). Operative setup utilizing frameless neuronavigation and a surgical microscope with the patient's head positioned 180° away from anesthesia to facilitate intraoperative MRI (iMRI) scanning (**f**, **g**). iMRI suite and scanner (**h**). Coronal T2W image from initial iMRI demonstrates residual tumor (**i**). Coronal T2W image from second iMRI after further resection demonstrates a gross total resection (**j**)

the magnetic fields created by bioelectrical currents as a result of neuronal activation and is, therefore, a direct marker of neuronal activity. Navigated TMS uses a magnetic field to induce a cortical electrical field and thus elicits or inhibits neuronal activity. A single pulse is used to elicit a motor response, or repetitive pulses are used to inhibit language function thereby mapping functional motor and language areas that are sufficient—and possibly necessary—to evoke a physiological response. DTI is the only preoperative method for visualizing subcortical white mater tracts (Fig. 2.3) (Choudhri et al. 2014b). All of these functional imaging techniques are more accurate for mapping motor areas than language areas.

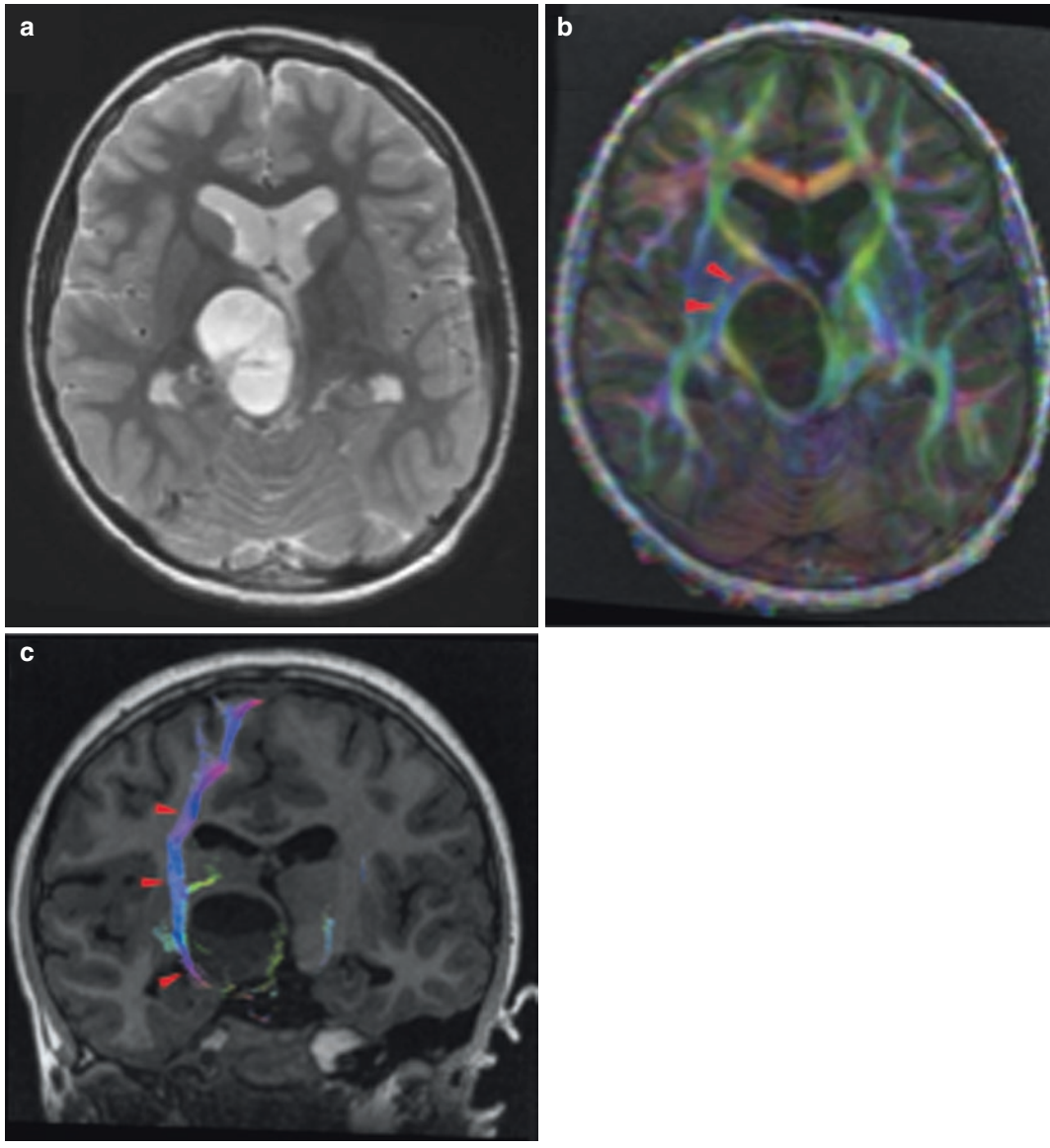

Fig. 2.3 Axial T2W image in a 5-year-old male shows a multicystic lesion centered in the right cerebral peduncle, consistent with a thalamopeduncular glioma (**a**). Axial T1W image with overlay of DTI data shows anterolateral displacement of the posterior limb of the internal capsule (red arrowheads) (**b**). Coronal T1W image with "tractography" overlay shows the course of the fibers of the corticospinal tract along the lateral aspect of the lesion (*red arrowheads*) (**c**)

2.2.6 Preparation for Tumor Resection: Neoadjuvant Chemotherapy

In some tumors found in newborns, infants, and young children, the risk of excessive blood loss with resection is great; the best example of this is choroid plexus carcinoma. Infants have small blood volumes; transfusing multiple blood volumes can lead to coagulopathy and electrolyte imbalance. Therefore, these patients may be best served by first treating the tumor with chemotherapy (i.e., neoadjuvant chemotherapy) before pursuing resection. Tumors will often shrink and become cystic and the reduction in vascularity is notable, resulting in safer and more complete tumor removal (Iwama et al. 2015; Van Poppel et al. 2011).

2.2.7 Preparation for Tumor Resection: Family Counseling

One of the most important steps in preparing a pediatric patient for a brain tumor resection is talking with the parents and family about the patient's prognosis, the risks, and the goals of surgery without overwhelming and confusing them with statistics and medical terminology. While there are general risks associated with any craniotomy, such as bleeding and wound infection, it is more important to stress the potential—or even anticipated—neurologic deficits specific to the location and size of the tumor. Neurologic injury may occur as a result of the surgical approach or during extirpation of the mass. Examples include Parinaud's syndrome with a pineoblastoma, posterior fossa syndrome in a young boy with a medulloblastoma, or cranial neuropathies with a cerebellopontine angle ependymoma. It is usually easier for the family to psychologically deal with new postoperative neurologic deficits if they've learned about them before surgery. It is equally important to define the expectations of surgery, such as total resection, subtotal resection, or biopsy, as well as the potential need for further surgical procedures (e.g., ventriculoperitoneal shunt, feeding tube), therapies (e.g., physical, speech), and expected length of hospital stay.

2.2.8 Preparation for Tumor Resection: Teamwork

Orchestrating a successful surgery requires the integration of multiple individuals and services, including anesthesiology, operating room nurses and technologists, and neuroradiology for intraoperative MRI cases. It is important to have a preoperative "huddle" with all team members to discuss positioning, need for vascular access, estimated length of surgery, anticipated blood loss, specific blood pressure management, need for any intraoperative neuromonitoring, and airway management (i.e., whether the patient will be extubated or remain intubated after surgery). One way to set a preoperative threshold for blood transfusion is to define the maximal allowable blood loss. Maximal allowable blood loss is the estimated blood volume of the patient multiplied by the difference between the patient's starting and minimal allowable hematocrits, divided by the starting hematocrit. For example, a 5 kg infant with an estimated blood volume of 75 cc/kg, a starting hematocrit of 30, and a minimal acceptable hematocrit of 22 would have a maximal allowable blood loss of approximately 100 cc. If further bleeding is anticipated, transfusion of blood should be initiated.

2.3 Tumor Resection

In this section we will discuss surgical management and approaches to the more common locations and types of pediatric brain tumors, such as the pineal region/posterior third ventricle, posterior fossa, and suprasellar area. Each child's brain tumor is unique; in many respects, its surgical management should be as well. Much of what can be done by the neurosurgeon depends on the age of the child, the type of tumor, its location and therefore the risks associated with resection, and whether or not there are local or distant metastases. For many nonmetastatic childhood

intracranial neoplasms, the goal of initial surgery is complete resection (i.e., gross total resection (GTR)), defined as no conclusive evidence of residual tumor on the intra- or immediate postoperative MRI, when deemed feasible. Such philosophy applies to tumors like medulloblastoma, ependymoma (infra- and supratentorial), primitive neuroectodermal tumor (PNET), and virtually all low-grade tumors.

Intraoperative magnetic resonance imaging (iMRI) has revolutionized surgical management of pediatric brain tumors by allowing the surgeon to confirm a gross total resection, while the patient is still under general anesthesia and their wound is open (Choudhri et al. 2014a, 2015b). This high-dollar technology greatly reduces the risk of having to take the child back to the operating room for continued resection, but with the drawbacks of added operating room (OR) time, challenges in interpreting the intraoperative images, and significant new safety issues (Shah et al. 2012). It also requires close cooperation and communication with the anesthesiology team, MR technologist, OR safety officer, and neuroradiologist.

2.3.1 Posterior Fossa (Excluding Brainstem Tumors)

The posterior fossa, as mentioned previously, is a common site for pediatric tumors. The "big 3" tumors are medulloblastoma, ependymoma, and pilocytic astrocytoma. Each has their own unique imaging features. Medulloblastomas and ependymomas are typically found within the 4th ventricle, whereas pilocytic astrocytomas are most often located within the cerebellum (i.e., the vermis or hemispheres). Medulloblastomas are hypercellular and therefore appear hyperdense on the initial CT. Pilocytic astrocytomas often have a cystic component with enhancing nodule(s). Ependymomas classically project through the foramen Luschka into the cerebellopontine angle, or through the foramen magnum into the cervical spinal canal (i.e., "plastic ependymoma"). Midline or fourth ventricular tumors are approached via a standard midline suboccipital craniotomy, whereas hemispheric tumors require a lateral suboccipital approach. Although we have seen the dawn of a new era in which tumors are being classified at the molecular level, resulting in subclassification and novel "targeted" chemotherapeutic options, the surgical goal of these tumors remains maximal safe resection (Gajjar et al. 2014).

2.3.2 Brainstem Tumors

Brainstem tumors can be broadly categorized as being radiographically focal or diffuse/infiltrative (Green and Kieran 2015). The classic example of an infiltrative pediatric brainstem tumor is a diffuse intrinsic pontine glioma (DIPG). Children with these tumors are typically young and present with a combination of long-tract and cranial nerve findings. DIPG is a radiographic diagnosis, surgery is relegated to the management of hydrocephalus, and the only known treatment that has some effect, albeit temporary, is radiation (Bredlau and Korones 2014). For pontine tumors that are "atypical" in appearance, a biopsy is warranted. Focal tumors are more often low-grade, and most commonly are pilocytic astrocytomas. All focal tumors (with the exception of tectal gliomas), whether benign or malignant, should be considered for resection (Klimo et al. 2013, 2015a). Tectal gliomas have a well-known indolent biologic behavior, and like DIPG, surgery is limited to the treatment of hydrocephalus. Resection of focal brainstem tumors requires careful planning, high-quality preoperative imaging (including tractography), and detailed discussions with the parents on what neurologic deficits to expect.

2.3.3 Pineal Region/Posterior Third Ventricle

There is a wide variety of tumors that may arise in this region of the brain; examples include pineoblastoma and germ cell tumors (Fig. 2.4). Because these patients often present with obstructive hydrocephalus secondary to occlusion of the

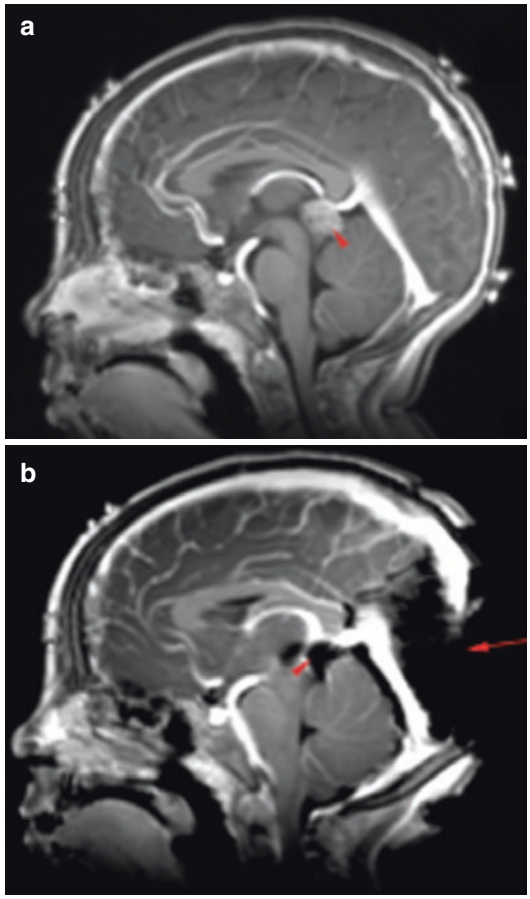

Fig. 2.4 Sagittal T1W + C image in a 2.5-year-old girl with a history of bilateral retinoblastoma shows an enhancing pineal mass (red arrowhead), consistent with a "tri-lateral" retinoblastoma (**a**). Sagittal T1W + C image from an iMRI scan shows successful resection of the tumor (*red arrowhead*). Note the open craniotomy (*red arrow*), which would have facilitated further resection, if needed (**b**)

aqueduct of Sylvius, surgical management is most often directed at treating the hydrocephalus by way of an endoscopic third ventriculostomy, obtaining cerebrospinal fluid (CSF) for germ cell markers (i.e., beta human chorionic gonadotropin, alfa fetoprotein), and angling the endoscope posteriorly to obtain tissue for biopsy. If the germ cell markers are elevated, then by definition the child has a non-germinomatous germ cell tumor (e.g., choriocarcinoma, endodermal sinus tumor) and initial treatment is chemotherapy. If the germ cell markers are negative and the biopsy is consistent with a germinoma, then the child is treated with radiation with or without chemotherapy with a very high chance of cure, even with metastatic disease. A nondiagnostic biopsy with negative CSF markers usually requires an open biopsy. The three surgical approaches that we use to resect or biopsy tumors in the pineal region/posterior third ventricle are the supracerebellar-infratentorial, the occipital-transtentorial, and the posterior transcallosal (Kennedy and Bruce 2011).

2.3.4 Sellar/Suprasellar

The two most common suprasellar tumors in children are craniopharyngiomas and optic pathway-hypothalamic astrocytomas. Children who present with diabetes insipidus (DI) and an enhancing mass along the pituitary stalk or hypothalamic region typically have one of two pathologies: germinoma or eosinophilic granuloma (histiocytosis X). It is exceedingly rare for optic pathway-hypothalamic astrocytomas or craniopharyngiomas to present with DI. Pure sellar lesions are rare, but may include craniopharyngioma, micro- or macroadenomas (functioning or non-functioning) in older children, and the non-neoplastic Rathke's cleft cyst.

Controversy continues among neurosurgeons as to the role of surgery with craniopharyngiomas. There are those who feel that craniopharyngiomas should be maximally resected without adjuvant therapy (Elliott et al. 2010); others believe in a less aggressive surgical approach in order to avoid significant morbidity (i.e., neurologic, endocrine, or cognitive dysfunction) followed by radiotherapy (Klimo et al. 2015b). We generally ascribe to the latter philosophy. Purely cystic craniopharyngiomas can be treated with placement of an Ommaya catheter to aspirate the tumor cyst, followed by radiotherapy or the injection of intracystic chemotherapy (e.g., bleomycin), immunotherapy (e.g., interferon), or radioactive agents (e.g., P-32) (Cavalheiro et al. 2010; Mottolese et al. 2001; Zhao et al. 2010). Surgical approaches for craniopharyngiomas are dictated by the location of the tumor (Fig. 2.5) and include subfrontal, transsylvian, and anterior

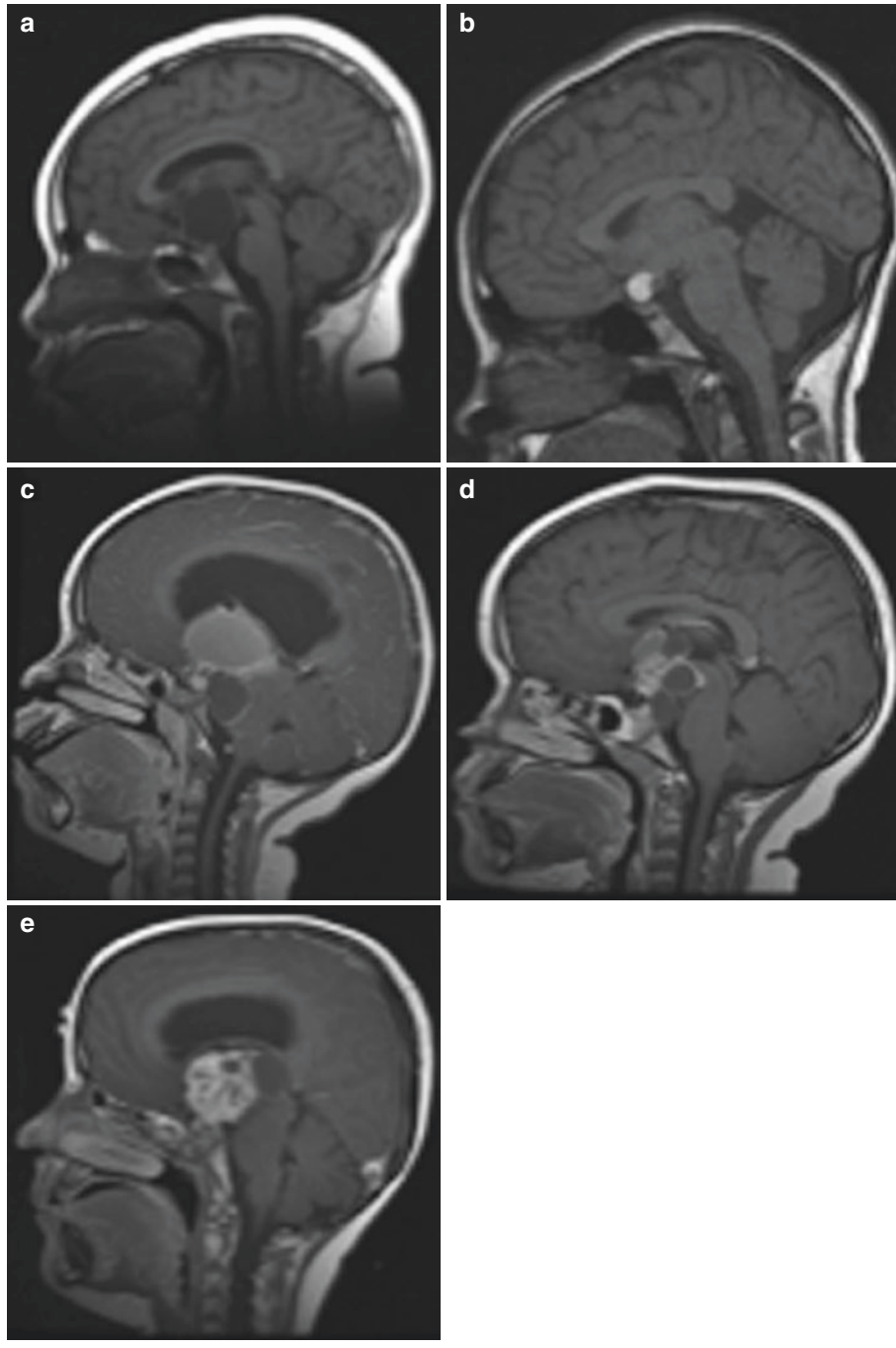

Fig. 2.5 The variety of imaging appearances of craniopharyngioma. This variety underscores the need for patient-specific surgical and treatment plans. Sagittal T1W image shows a cystic suprasellar lesion (**a**). Sagittal T1W image shows a suprasellar cystic lesion with intrinsic T1 hyperintense signal, representing proteinaceous secretions (**b**). Sagittal T1W image post contrast shows a multicystic suprasellar lesion with enhancing rims, with the components having different central T1 characteristics related to different proteinaceous contents (**c**). There is also caudal retroclival extension. Sagittal T1W image post contrast shows a central solid enhancing component with multiple smaller cystic components (**d**). Sagittal T1W image post contrast shows a large central solid enhancing component, with several internal cystic areas and a single posteriorly directed cyst within the third ventricle (**e**)

transcallosal approaches. Intrasellar craniopharyngiomas can be resected through a transnasal-transsphenoidal route, using a microscope or endoscope (Jane et al. 2010).

Optic pathway-hypothalamic tumors are generally not thought to be curable by surgery alone, except in the rare case of a prechiasmatic optic nerve glioma with no functional vision. These tumors originate from non-resectable areas of the brain and can often be diagnosed by imaging alone. They are associated with neurofibromatosis type I (i.e., von Recklinghausen disease). Surgery is reserved for biopsy or subtotal resection in those cases where there is significant symptomatic mass effect or where the tumor has caused obstructive hydrocephalus by growing cephalad into the third ventricle (Goodden et al. 2014). The primary treatment modalities for these tumors are chemotherapy and/or radiotherapy. The same approaches used for craniopharyngioma can be used for this tumor, with the exception of the transnasal approach.

2.3.5 Supratentorial

The goal of surgery for most supratentorial tumors should be maximal resection. Extraaxial tumors, such as meningiomas, are rare in children. As previously discussed, functional imaging modalities should be used in cases where the tumor is in close proximity to eloquent areas (Fig. 2.2). Awake craniotomy is difficult to perform in a child, so we rely heavily on these preoperative mapping tests. For a child whose tumor cannot be completely resected but who has debilitating seizures as a result of it, surgery to resect the epileptogenic part of the tumor (e.g., temporal lobectomy) can have a substantial positive impact on the quality of that child's life.

2.4 Postoperative Care

After tumor resection, patients are brought to the intensive care unit (ICU) for close neurologic and cardiorespiratory monitoring. Almost all patients are extubated while still deeply sedated in the OR so as to avoid any coughing or bucking as they awaken with the endotracheal tube in place and during transport to the ICU. Such reflexes can rapidly increase the patient's systemic blood pressure and intracranial venous pressure, which could lead to hemorrhage within the fresh resection cavity, especially if there is a raw, residual tumor surface. For excessively long cases or those with high volume fluid resuscitation, extubation may be delayed until neurologic and cardiopulmonary systems are assessed and stabilized.

The most common immediate postoperative issues that require close monitoring are intracranial hemorrhage, seizure, hydrocephalus, and endocrinologic derangements. Strict blood pressure control is paramount since postoperative hypertension can result in hemorrhage within the resection cavity (Basali et al. 2000). Prompt and adequate treatment for pain and agitation often improves the patient's blood pressure. A maximum allowable systolic blood pressure is typically set for the first 24–48 h after surgery, followed by gradual relaxation of the parameter. The blood pressure limit is age dependent, but an oft-recommended limit is less than 140 mmHg. We consider a nicardipine drip an easy and effective method of titrating the patient's blood pressure. Hypotension is to be avoided, particularly in cases in which there was significant brainstem or spinal cord compression by the tumor, or if there was manipulation/dissection of major arteries so as to maintain adequate tissue perfusion. Patients should be kept euvolemic to mildly hypervolemic.

As discussed previously, obstructive hydrocephalus is a common presenting condition in children with brain tumors. Our general approach to such children is to resect the tumor in order to relieve the hydrocephalus, which we are successful in achieving in many cases. Mechanisms of post-resection hydrocephalus include obstruction from residual tumor and subarachnoid block caused by leptomeningeal metastasis, operative blood products, or proteinaceous CSF. All patients with preoperative hydrocephalus, or who are at risk of developing hydrocephalus postoperatively (e.g., intraventricular tumor), need to be carefully monitored for persistent or new hydrocephalus,

respectively. Such evidence would include increase in ventricular size, inability to wean an external ventricular drain (EVD), development of a new or growing subdural hygroma or pseudomeningocele, and clinical changes, such as irritability, headaches, emesis, full fontanelle, or depressed level of arousal. Postoperative hydrocephalus is treated with either an EVD, a shunt, or ETV.

The Canadian Preoperative Prediction Rule for Hydrocephalus (CPPRH) was devised in an attempt to identify patients before resection who are at risk for post-resection hydrocephalus (Riva-Cambrin et al. 2009). Variables predictive of post-resection hydrocephalus include age less than 2 (score of 3), papilledema (score of 1), moderate to severe hydrocephalus (score of 2), cerebral metastasis (score of 3), and specific estimated tumor pathologies (score of 1). A total score of ≥5 places the patient at high risk. Estimated preoperative tumor pathologies based on imaging and clinical information that qualify for a score of 1 include medulloblastoma, ependymoma, and dorsally exophytic brainstem glioma. The modified CPPRH also adds the presence of transependymal edema as a risk factor (Foreman et al. 2013). For children with favorable age (>2 years), pathology (e.g., tectal glioma, pineal tumors), anatomy, and site of CSF blockage (obstruction between the third ventricle and the interpeduncular cistern), ETV is preferred over shunting as shunts are generally viewed as life-long implants that come with high risk of one or more shunt malfunction(s) (Gupta et al. 2007; Vogel et al. 2013). In cases where ETV is not appropriate or if the ETV fails, then ventricular shunting is the sole option.

If the patient has a postoperative seizure and is not already on an AED, then electrolytes and blood glucose should be checked expeditiously and any abnormalities should be promptly corrected, especially low sodium and magnesium; a non-contrast CT scan of the head should be obtained to rule out any new hemorrhage, edema, or hydrocephalus and the patient should be given a bolus of an AED, such as phosphenytoin or levetiracetam (both ~ 20 mg/kg), followed by maintenance therapy. If the patient's seizure lasts more than 5 min or if multiple seizures occur without full neurologic recovery in the interictal period, then the patient is considered to be in status epilepticus, which is a medical emergency (Claassen et al. 2015).

Removal of sellar and suprasellar tumors, such as optic pathway gliomas or craniopharyngiomas, may lead to transient or permanent disruption of the hypothalamic-pituitary axis, and subsequent anterior and posterior pituitary lobe dysfunction. The endocrinopathies that are most problematic for neurosurgeons are the ones that can cause dramatic changes in the serum sodium level: central diabetes insipidus (DI), cerebral salt wasting (CSW), or the syndrome of inappropriate antidiuretic hormone release (SIADH). Central DI is caused by inadequate antidiuretic hormone release and results in excessive production of dilute urine and resultant hypernatremia. Urine output continuously exceeding 3 cc/kg/h with a specific gravity of 1.005 or less with a concurrent elevation in serum sodium above 145 is diagnostic. Without close monitoring of urine output and sodium levels in patients with or at risk for DI, sodium levels can easily exceed 160 mEq/L, resulting in severe dehydration, mental status changes, and seizures. The treatment is desmopressin and free water replacement titrated to the patient's urine output.

SIADH and CSW both cause hyponatremia. With severe hyponatremia (<125 mEq/L) or rapid drops in sodium, headache, confusion, seizures, and cerebral edema can occur. SIADH results from an abnormal release of antidiuretic hormone (ADH) in the absence of a physiologic osmotic stimulus, resulting in excess water retention. Patients are either hypervolemic from the retained water or sometimes euvolemic. Serum osmolality is low (<275 mOsm/kg of water) while the urine is concentrated (>100 mOsm/kg of water). Cerebral salt wasting also produces hyponatremia and low serum osmolality in the presence of concentrated urine; but unlike SIADH, patients are hypovolemic. Intracranial disease results in failure of the kidneys to conserve sodium by an unknown mechanism. The key difference is the treatment. Fluid restriction effectively corrects the hyponatremia caused by SIADH while volume replacement with

gentle sodium support treats CSW. In the setting of a malignancy, SIADH is more common. Cerebral salt wasting will also respond to a fluid challenge. Regardless of the etiology, if the hyponatremia is severe (Na < 125 mEq/L) or symptomatic (i.e., confusion, seizures or coma), then correction with hypertonic (e.g., 3%) saline is indicated. However, care must be taken not to correct the sodium too quickly. In general, if the sodium level changed rapidly then the patient can tolerate rapid correction. The serum sodium must be checked every 2–6 h. The goal is to correct the serum sodium 1–2 mEq/L/h and limit the correction to 8–10 mEq/L in 24 h. If the sodium is corrected too quickly, central pontine myelinolysis can rarely occur. Conversely, rapid correction of hypernatremia can cause or exacerbate cerebral edema.

Given the high frequency of posterior fossa tumors, posterior fossa syndrome (PFS) deserves special mention. It is a syndrome consisting of mutism, oromotor and oculomotor apraxia, emotional lability, axial hypotonia, and cerebellar/brainstem dysfunction following resection of infratentorial tumors (Robertson et al. 2006). Risk factors include young age, male sex, large midline tumors, brainstem invasion, and medulloblastoma. It is thought to result from bilateral surgical damage to the proximal efferent cerebellar pathways (Patay 2015). Most patients wake-up from surgery with intact speech but develop mutism within 1–4 days after surgery. Most recover fluent speech within 4 months with average duration of 6 weeks. Recovery begins with clumsy and broken speech slowly progressing to full sentences. However, up to one-third of children will have lasting dysarthria after surgery. Irritability, inconsolable crying, impulsiveness, and disinhibition are the most frequent changes in affect. IQ and school performance are also affected, more commonly when the deep cerebellar nuclei are damaged. Treatment generally requires prolonged rehabilitation, including physical, occupational, and speech therapy. Overall, improvement is universal but the degree of recovery is variable. Mutism and emotional lability are generally transient but long-term cognitive and motor deficits are frequently recognized in these children.

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