Brainstem Tumors in Children

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Ali S. Haider, James M. Drake, and James T. Rutka

20.1 Introduction

Brainstem tumors are a disparate group of tumors that span the regions of the midbrain to the cervicomedullary junction (Fig. 20.1). They most frequently occur in children and lack a specific gender predilection. Over the past two decades, we have become increasingly more familiar with their characteristic patient symptom complex, their specific neuroimaging features, and a standardized approach to therapy. That said, there are still a number of challenges that are posed by tumors in this critical region of the neuraxis. As each tumor subtype could be the subject of an independent chapter, here, we will review the main patient presentations, the key neuroimaging features, and the goals of surgical and non-operative therapies for children with brainstem tumors.

A. S. Haider · J. M. Drake
Division of Neurosurgery, The Hospital for Sick Children, Toronto, ON, Canada
e-mail: haider@medicine.tamhsc.edu; james.drake@sickkids.ca

J. T. Rutka (✉)
Division of Neurosurgery, The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON, Canada

Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: james.rutka@sickkids.ca

20.2 Midbrain Tumors

20.2.1 Tectal Gliomas

20.2.1.1 Clinical Symptoms and Signs

Tectal gliomas are located in close proximity to the Sylvian aqueduct, and as such, they most often cause hydrocephalus from aqueductal obstruction. Accordingly, children will demonstrate clinical evidence of increased intracranial pressure, including papilledema, nausea, vomiting, headache, visual changes, and/or oculomotor deficits. Rarely, patients may also exhibit signs of ataxia, pyramidal tract dysfunction, and/or other cranial nerve palsies including nystagmus, tremor, diplopia, and Parinaud's syndrome [1].

20.2.1.2 Diagnostics

MRI is considered the gold standard imaging modality for diagnosis of these tumors. Computed tomography (CT) may often miss these lesions as they are isodense to the surrounding brain. Tectal tumors are best appreciated on T2 and FLAIR MR images in which a classic periaqueductal hyperintensity is seen (Fig. 20.2). In the majority of circumstances, tectal tumors are non-enhancing lesions. However, on occasion, they may be dorsally exophytic, cystic, and quite large (Fig. 20.3).

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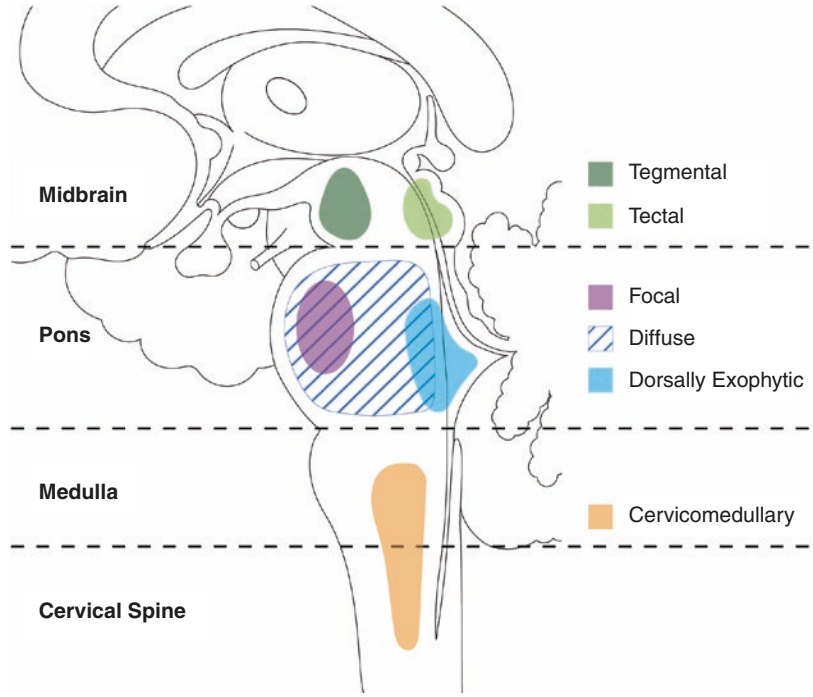

Fig. 20.1 The classification of brainstem tumors in children. Tumors in the brainstem can arise from the midbrain (tectal and tegmental), the pons (focal, diffuse, and dorsally exophytic), and the cervicomedullary region. This classification system has largely been derived from experience with localization of these tumors on imaging studies, particularly MRI

20.2.1.3 Staging and Classification

Tectal tumors can be classified into three groups based on MR appearance and subsequent correlation with neuroendoscopic, histopathologic, and postoperative clinical findings. Group 1 tectal tumors appear on MRI typically as a bulbous tectal mass, isodense on T1-weighted images, and hyperdense on T2-weighted images without gadolinium. Group 2 tectal tumors appear similar to Group 1 along with exophytic growth into the Sylvian aqueduct, further extending into the midbrain tegmentum and diencephalon. Group 3 tectal tumors typically appear as large lesions with mixed intensities on T1-weighted and T2-weighted images along with enhancement on gadolinium. These tumors typically exhibit exophytic growth into the Sylvian aqueduct and third ventricle.

20.2.1.4 Treatment

The preferred management of the majority of children presenting with tectal tumors is endoscopic third ventriculostomy (ETV) to overcome the obstruction of the aqueduct and to permit more physiological cerebrospinal fluid (CSF) drainage [2]. Ventriculoperitoneal (VP) shunting may be required, especially in children less than 1 year of age; however, this can be fraught with complications related to overdrainage in the setting of a child with established macrocephaly. After hydrocephalus is controlled, serial MR imaging is recommended on an annual basis for both ETV-treated and VP-shunted patients. ETVs are known to occlude on occasion requiring repeat fenestrations [3]; and VP shunts may block or disconnect in long-term follow-up. Direct surgical resection of the typical tectal tumor should not be performed. Atypical tectal tumors demonstrating serial growth and enhancement may require a neurosurgical approach, typically an infratentorial supracerebellar, or occipital transtentorial approach. On occasion, intensity-modulated radiation therapy (IMRT) or chemotherapy may be indicated for some of these latter types of tectal tumors.

20.2.1.5 Prognosis/Quality of Life

Children with tectal tumors whose hydrocephalus is well controlled can lead normal lives without significant cognitive or neurodevelopmental issues. The prognosis is typically excellent, although lifelong monitoring of hydrocephalus may be required.

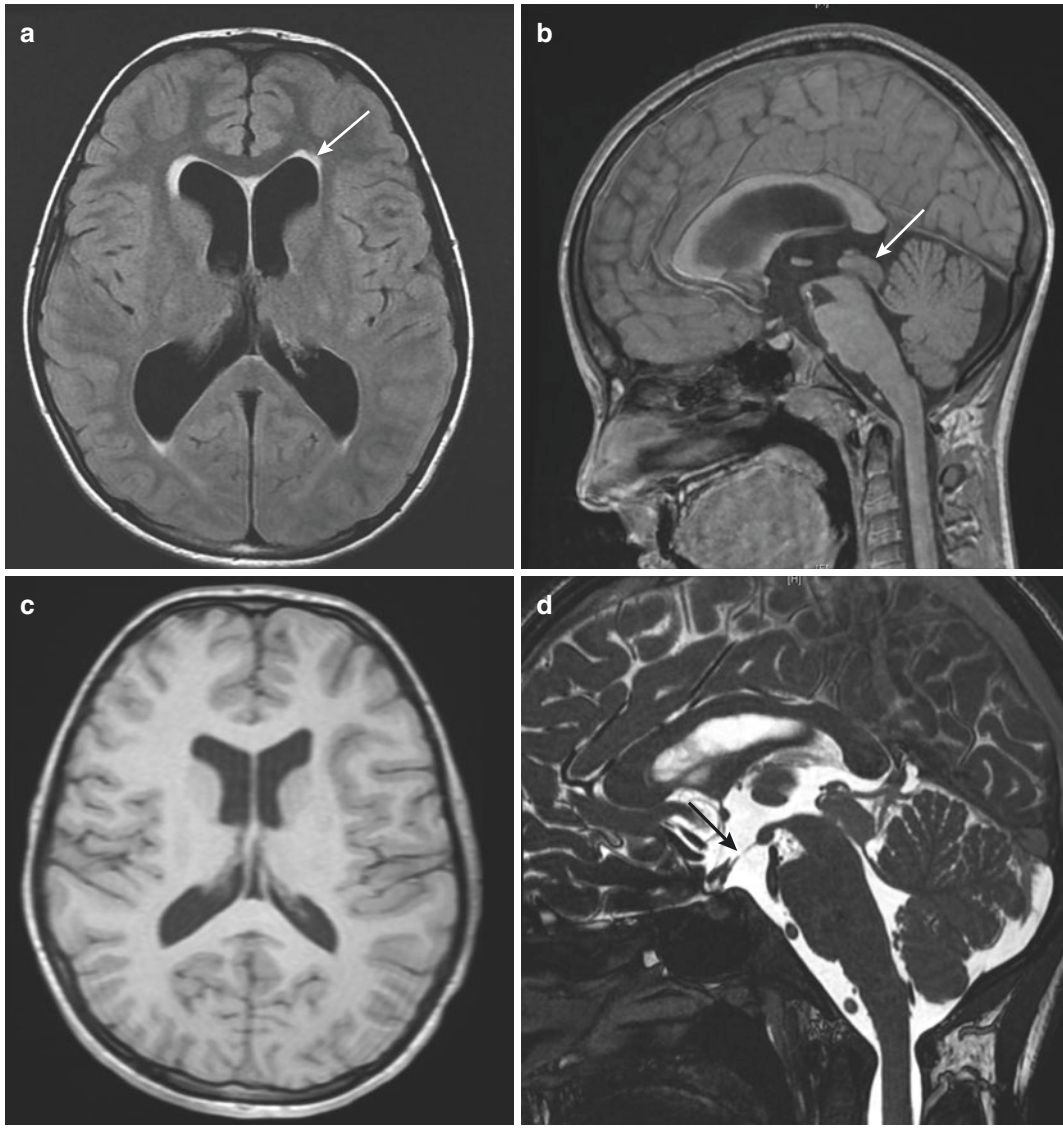

Fig. 20.2 Tectal glioma in an 8-year-old male complaining of headache and vomiting over 6 weeks. (**a**) Axial FLAIR MRI showing enlarged ventricles and periventricular high signal indicative of edema (arrow). (**b**) Sagittal T1 MRI showing mass in tectum creating obstructive hydrocephalus (arrow). (**c**) After endoscopic third ventriculostomy (ETV), the ventricles are smaller, the sulci are seen better, and there was CSF seen over the convexities. (**d**) After ETV, there is now a flow void seen through the third ventricle on the FIESTA MR imaging, indicative of patency of the ventriculostomy (arrow)

20.2.2 Tegmental Tumors

20.2.2.1 Clinical Symptoms and Signs

Tegmental tumors are focal midbrain tumors that typically arise in children less than 14 years of age. They cause symptoms by virtue of their mass effect on the unilateral tegmentum and corticospinal tract causing hemiparesis, oculomotor nerve palsy, and ataxia [4]. In most cases, symptoms can be traced back 6–12 months prior to diagnosis. Occasionally, unilateral tremor is seen, especially in those tumors where extension into the basal ganglia and thalamus are also noted.

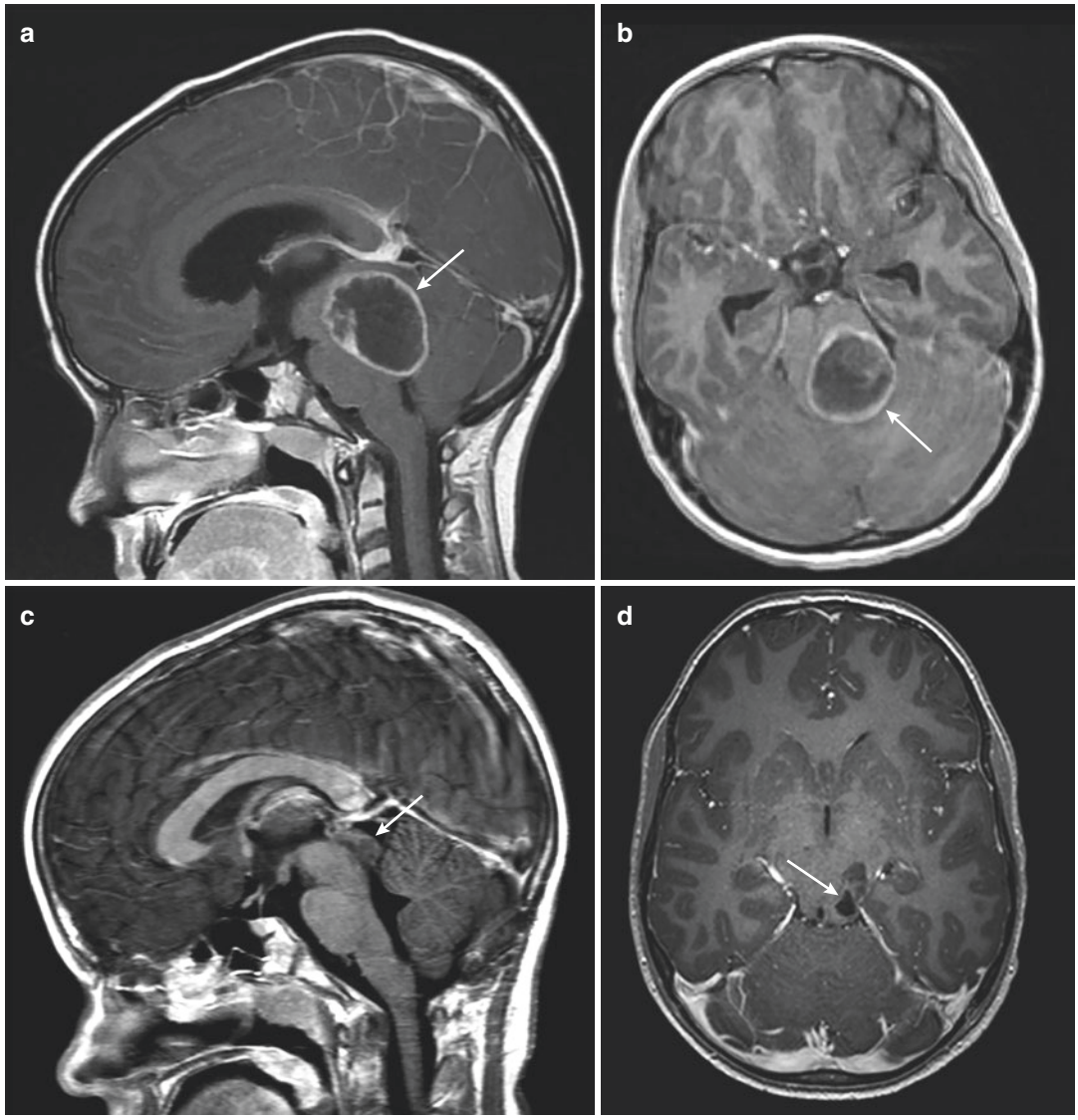

Fig. 20.3 Large, atypical tectal glioma in a 13-year-old male with neurofibromatosis type 1, headache, and vomiting. (**a**) Sagittal contrast-enhanced T1 MRI showing large posterior fossa cystic mass lesion with epicenter in the tectal region (arrow). (**b**) Axial MRI contrast-enhanced MRI depicting extent of involvement of the tectum and the fourth ventricle (arrow). (**c**) Following posterior fossa craniotomy, drainage of the tumor cyst, and removal of the cyst capsule, only small deformation of the tectum is still seen on this T1-weighted contrast-enhanced MRI scan (arrow). (**d**) Postoperative T1-weighted axial MRI with contrast demonstrating origin of the tumor from the tectal region without mass effect (arrow)

20.2.2.2 Diagnostics

The imaging modality of choice is MRI. Tegmental tumors are typically homogeneously enhancing lesions upon the administration of gadolinium (Fig. 20.4). They can be quite large occupying the entire tegmentum and can cause hydrocephalus by virtue of occlusion of the foramina of Monro.

20.2.2.3 Staging and Classification

There is no uniform staging or classification system for midbrain tegmental tumors. Rather, it is

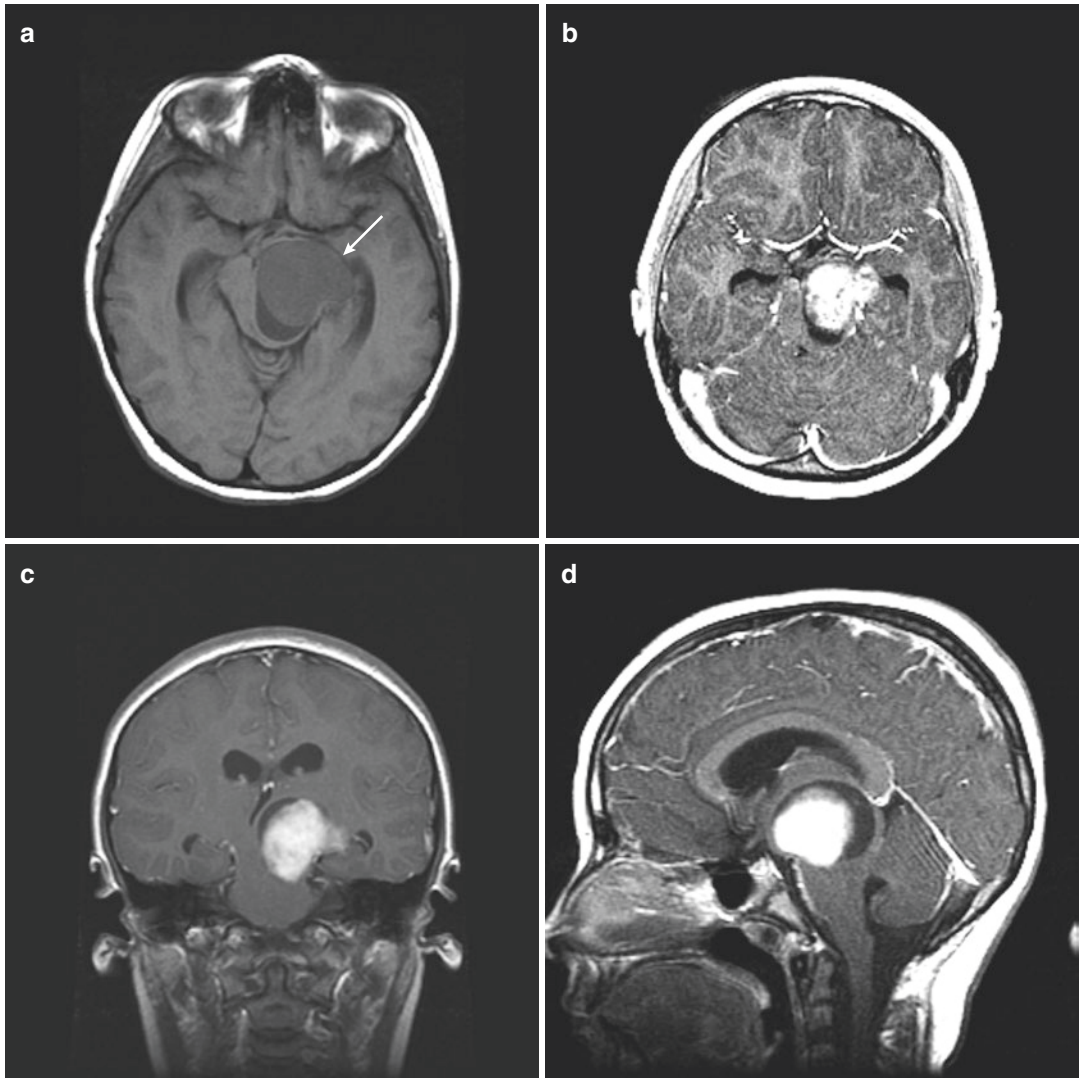

Fig. 20.4 A 12-year-old female with 3-month history of progressive right-sided weakness and ataxia. (**a**) Axial T1 MRI showing mass lesion occupying the left tegmental region of the brainstem (arrow). (**b**) Following contrast administration, the lesion avidly enhances homogeneously. (**c**) Coronal T1 MRI with contrast showing large lesion arising from the left midbrain tegmentum with extension into the thalamus. At times, these lesions are called "thalamopeduncular" lesions. (**d**) Sagittal T1 MRI with contrast demonstrating large, central enhancing mass lesion which typifies focal midbrain gliomas

known that these lesions may extend from the tegmentum to involve the thalamus and are sometimes called "thalamopeduncular" lesions [5].

20.2.2.4 Treatment

Focal tegmental tumors present formidable challenges to the neurosurgeon in terms of approach and long-term management. The majority of lesions are low-grade gliomas. Biopsy can be performed, either framed based or frameless. Options for surgical approaches include trans-Sylvian, transtemporal, or transcallosal depending on the size of the tumor and its presentation to the pial or ventricular surfaces (Fig. 20.5) [5, 6]. Optimal neurosurgical resection is aided through the use of neuronavigation particularly with diffusion tensor

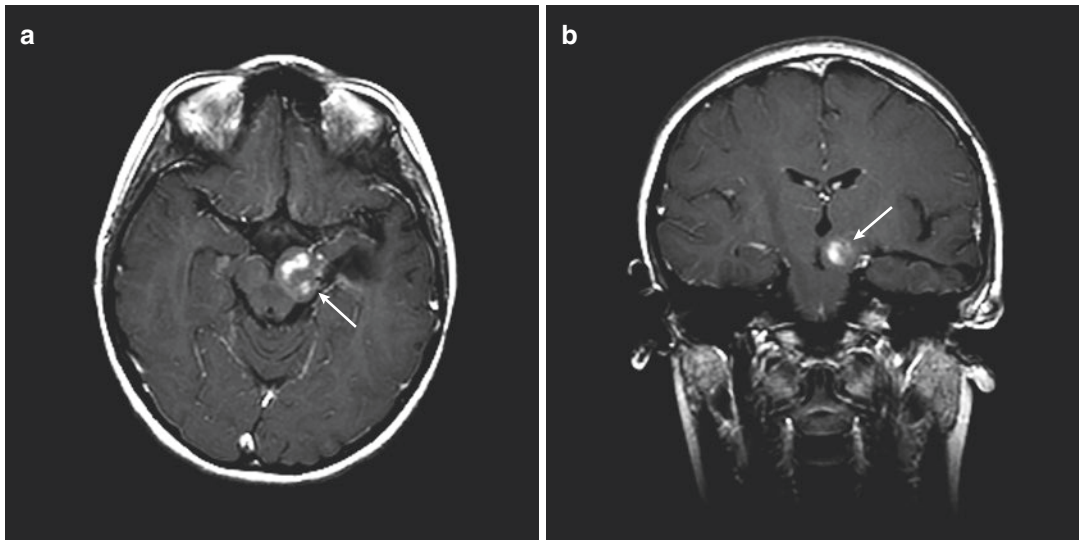

Fig. 20.5 Postoperative MRI in child whose images are shown in Fig. 20.3. A left middle temporal gyrus approach to the lesion was undertaken following temporal craniotomy. Neuronavigation was used to identify the equator of the tumor; and the cavitron was used to debulk the lesion. (**a**) Axial T1 contrast-enhanced MRI showing trajectory to the tumor and small residual that occupies the left tegmentum. (**b**) Coronal MRI with contrast depicting the tract leading from the middle temporal gyrus to the midbrain tumor and small residual. This patient went on to receive chemotherapy in follow-up, and no further surgery was required. There was no new neurological deficit, but transient dysphasia for 2 weeks after surgery

imaging sequences on MR, intraoperative neuronavigation, and intraoperative MRI scanning [7] (Fig. 20.6). The goal of surgery is to achieve a gross total resection of the tumor. Where this is not possible, then a trial of chemotherapy using specific midline low-grade glioma drug therapy becomes possible [6]. At times the BRAF gene may be mutated or fused in low-grade astrocytomas, and this molecular finding offers an opportunity for targeted drug therapy [8]. However, standard low-grade glioma chemotherapy in children is also an option and works well in many instances [8]. If neurosurgical resection and chemotherapy are not sufficient, then intensity-modulated radiation therapy (IMRT) can be delivered.

20.2.2.5 Quality of Life/Prognosis

Children with focal midbrain tumors can do extremely well after aggressive neurosurgical resection of their tumors. If there is residual tumor after surgery and demonstrated regrowth, then several options exist for targeted chemotherapy, conventional chemotherapy, or radiation therapy in older children. With maximum safe surgery, most children with focal midbrain tumors can lead normal lives. By virtue of the potential for recurrence, serial MR imaging is highly recommended. Overall, the prognosis is good for children with focal midbrain tumors with 90% or higher survival rates at 5 years [5].

20.3 Pontine Tumors

Tumors of the pons in children will typically be gliomas of varying grade malignancy. They can be divided into diffuse intrinsic pontine glioma (DIPG), dorsally exophytic, or focal pontine tumors, based primarily on the neuroradiological findings. Here we will cover DIPG and dorsally exophytic pontine gliomas.

20.3.1 Diffuse Intrinsic Pontine Glioma (DIPG)

DIPGs comprise approximately 70% of all brainstem tumors making them the most common

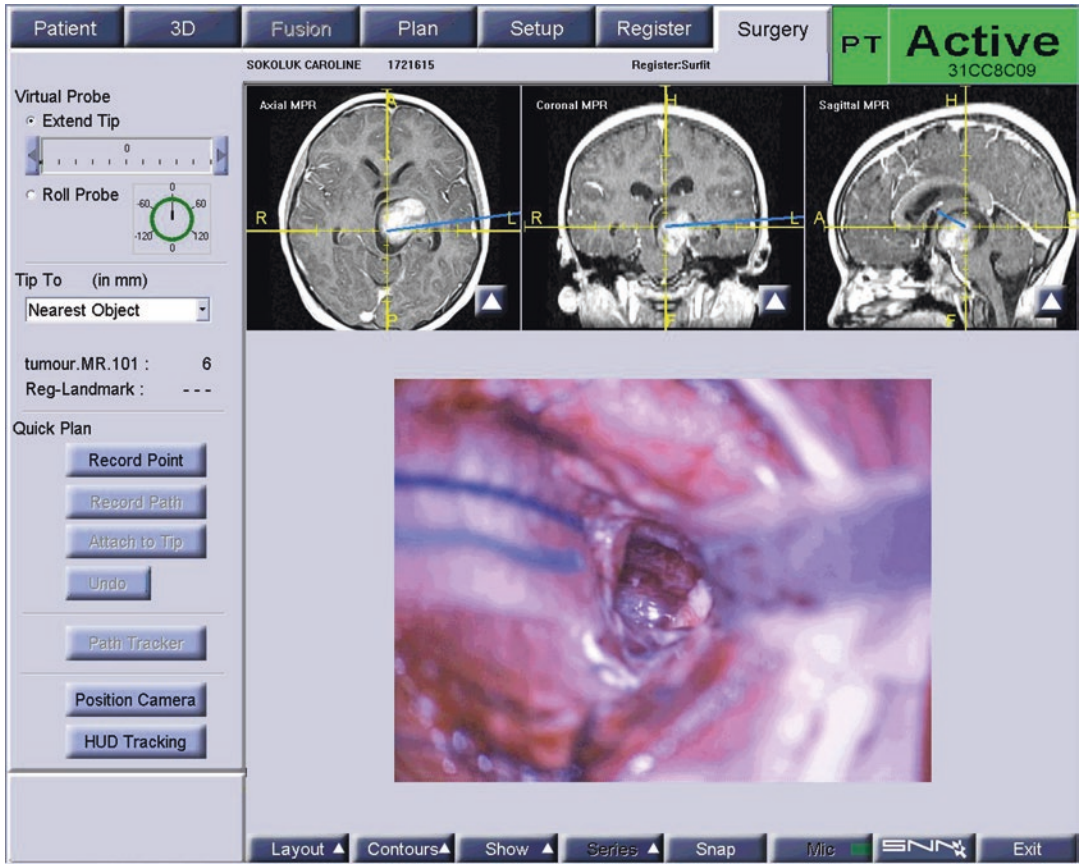

Fig. 20.6 Intraoperative screensaver of case of focal midbrain tumor shown in Figs. 20.3 and 20.4 demonstrating depth of resection with neuronavigation and small corridor of entry through the middle temporal gyrus

form of brainstem tumor. Typically these lesions are high-grade neoplasms, and overall survival is very poor with most children succumbing within 2 years of diagnosis despite all forms of therapy [9]. There is equal sex incidence of DIPGs, and most children are between ages 5 and 10 at time of diagnosis. Interestingly, the molecular genetics of DIPG in childhood are now rather well worked out with novel genetic pathways being identified as drivers of this tumor including ACVR1, H3K27M, PDGB, and several others [10, 11] (Fig. 20.7).

20.3.1.1 Clinical Symptoms and Signs

There is often a rapid appearance of clinical findings including cranial nerve deficits (e.g., facial nerve palsy, VIth nerve palsy causing diplopia), long tract signs, and ataxia. Hydrocephalus may form causing headaches and a syndrome of raised intracranial pressure, but this is usually a late presenting feature in the course of the disease [9].

20.3.1.2 Diagnostics

The diagnosis of DIPG is most often made by MRI. Frequently, there is diffuse enlargement of the pons occupying 50–75% or more of this region of the brainstem. There may be exophytic components, especially ventrally. Contrast enhancement may exist but is usually patchy and contained within the diffuse swelling of the pons. At times, the basilar artery may be totally engulfed by tumor (Fig. 20.8). Other MR sequences and techniques have been used for DIPG, including MR spectroscopy (MRS) showing lower mean total choline concentration and diffusion tensor imaging (DTI), but these have

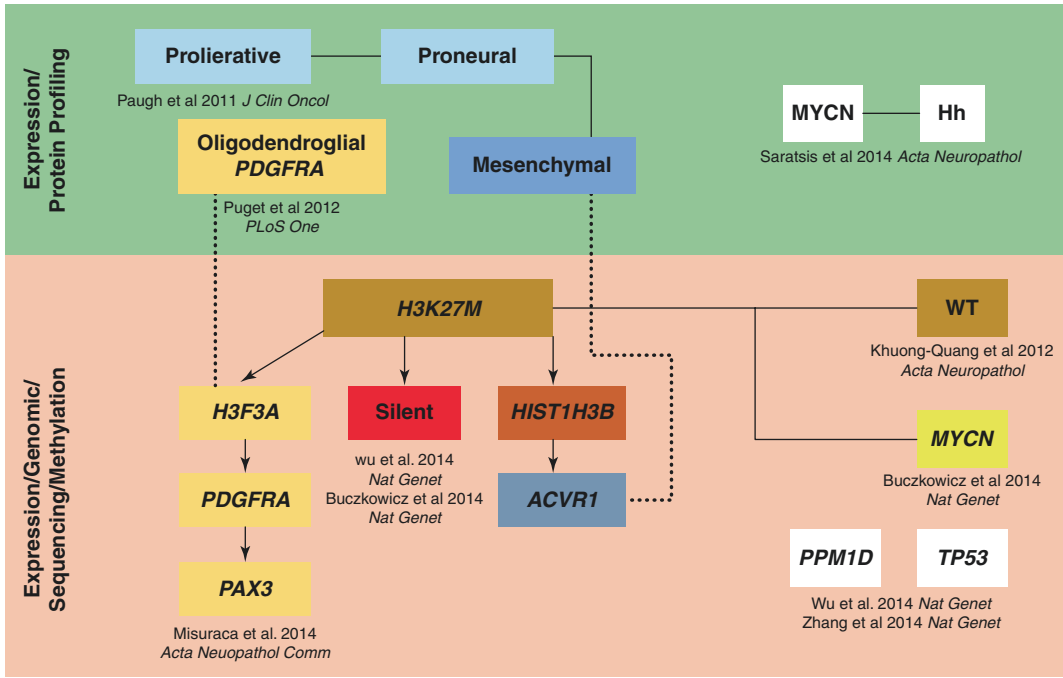

Fig. 20.7 Schematic of molecular genetic characterization of DIPGs. The main genetic drivers of DIPG include MYCN, ACVR1, H3K27M, PDGFRA, and PAX3, among several others (Adapted from Misuraca, Cordero, and Becher, Front Oncol 2015)

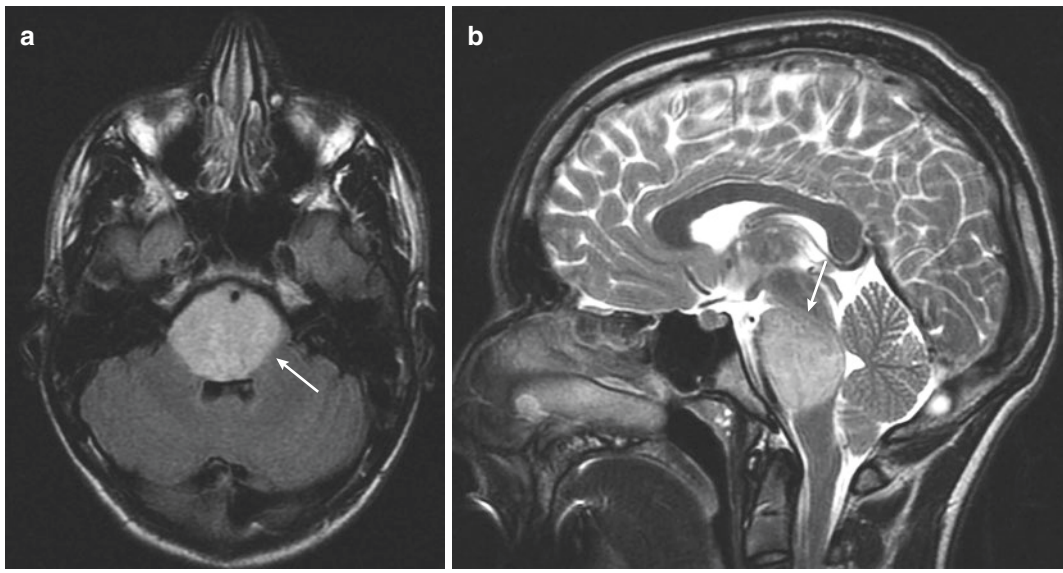

Fig. 20.8 MRI scan of a 14-year-old male with brief history of diplopia, ataxia, and left facial palsy. (**a**) Axial FLAIR MRI showing high signal occupying the entire pons (arrow). (**b**) Sagittal T2 MRI depicting extent of pontine involvement by DIPG (arrow)

not proven reliable in predicting neuropathology of the lesions or outcome.

20.3.1.3 Staging/Classification

There is no generally accepted staging system for children with DIPG. With disease progression, there may be metastases through leptomeningeal seeding to other regions of the brain or to the spinal axis.

20.3.1.4 Treatment

There is no role for direct surgery for the vast majority of children with DIPGs. In addition, for many years, the common practice was not to offer biopsy of DIPGs in children with typically appearing tumors on MRI. Children with a DIPG diagnosis on MRI would move quickly to radiation therapy protocols including the use of IMRT or hyperfractionated radiation therapy [9]. A number of clinical trials have now been performed assessing the role of chemotherapy in DIPG [12, 13]. Chemotherapeutics such as vincristine, CCNU, prednisone, cisplatin, cyclophosphamide, etoposide, and tamoxifen have all been tried but with limited to no effect.

With the recognition that some DIPGs may have atypical features (e.g., child older than 10 years, lateral enhancing tumor with less than 50% brainstem involvement), some centers are now offering stereotactic biopsies for these patients [14, 15]. Stereotactic biopsy can be performed safely, and in groups where molecular genetics can be performed on fresh tumor specimens, there are reasonable expectations of finding new or targetable genetic lesions [16].

Some innovative clinical trials are now being performed on children with DIPG. Souweidane and colleagues have recently published their findings on the use of convection-enhanced delivery (CED) of a radioimmunotherapy agent targeting the glioma-associated B7-H3 antigen, along with a number of other targeted agents, to treat children with DIPG [17–20]. They have shown that the use of CED in children who have already received radiation therapy is both safe and potentially efficacious [17]. In addition, some recent interesting studies have been done with immunotherapy. Benitez-Ribas et al. treated children with DIPG with autologous dendritic cells pulsed with an allogeneic tumoral cell line lysate. They showed that this protocol leads to a definitive immune-generated response and may serve as a promising backbone for future therapy [21]. We have recently shown that the use of magnetic resonance-guided focused ultrasound (MRgFUS) can increase the delivery of chemotherapeutics, specifically doxorubicin, to the brainstem in experimental models [22].

20.3.1.5 Prognosis/Quality of Life

The prognosis of children with DIPG remains poor despite intensive therapies. DIPGs remain highly chemo- and radio-resistant neoplasms. Children normally remain in remission for 6–8 months following the completion of radiation therapy. However, there are some harbingers of a poor prognosis, and these include age less than 2 years at tie of diagnosis, multiple cranial nerve palsies, and rapid onset of symptoms prior to diagnosis.

At times, quality of life is made possible only through the continued use of corticosteroids; however, these should be limited so that children do not suffer some of the feared side effects of these agents. Palliative care approaches should be offered at the time of clear tumor progression after all forms of therapy have been offered and have failed.

20.3.2 Dorsally Exophytic Pontine Gliomas

20.3.2.1 Symptoms and Clinical Signs

Dorsally exophytic pontine gliomas comprise roughly 20% of pediatric brainstem gliomas. They tend to present insidiously, with patients reporting minor symptoms over a 6–12-month time period. Some of the typical symptoms include headaches and vomiting; and ataxia, abducens or facial nerve palsies, and torticollis are some of the typical neurological signs [23].

20.3.2.2 Diagnostics

CT scans may still be used as a quick screening tool. On CT, these lesions are typically

hypodense and fill the fourth ventricle. Bright contrast enhancement may be evident as well (Fig. 20.9). MRI has become the standard assessment tool used for children with dorsally exophytic brainstem gliomas. On MRI, a cap of surrounding CSF may be seen dorsolaterally. Ventrally, the tumor will blend into the brainstem, and it is frequently difficult to ascertain where the tumor ends and where the functional components of the brainstem begin. Signal characteristics are of low signal on T1 with high signal on T2 sequences. The tumor edges will generally be consistent between T1 and T2 sequences as compared to diffuse intrinsic lesions where there usually is a larger area of T2 signal abnormality compared to T1. As with CT, there is usually bright enhancement following intravenous contrast administration (Fig. 20.10).

20.3.2.3 Staging and Classification

Dorsally exophytic gliomas are predominantly pilocytic astrocytomas, with rare occurrence of anaplastic, higher-grade lesions, or gangliogliomas. The most consistent area of growth is through the path of least resistance, through the ependyma of the fourth ventricle. These lesions are locally recurrent and rarely show signs of distant dissemination or metastasis.

20.3.2.4 Treatment

Due to modern advances in operative technology and neuroimaging, the majority of dorsally exophytic brainstem gliomas are quite amenable to surgical resection. Whereas these lesions were thought to be inoperable, today dorsally exophytic brainstem gliomas can be approached quite aggressively due to the advent of microneurosurgical techniques, intraoperative neuromoni-

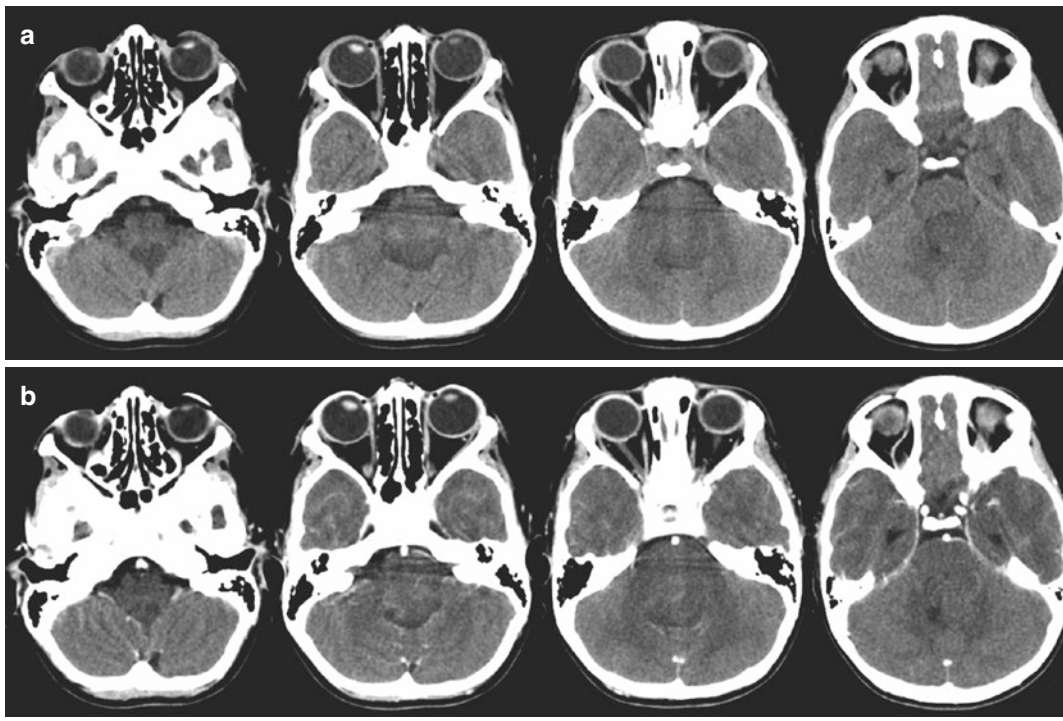

Fig. 20.9 CT scan of dorsally exophytic brainstem glioma in a 12-year-old male with 5-month history of increasing clumsiness, worsening ataxia, and diplopia. (**a**) Axial CT scan without contrast demonstrating subtle slightly low-density lesion filling the fourth ventricle. (**b**) Upon contrast administration, the lesion shows patch, inhomogeneous enhancement. The border of the lesion with the dorsal brainstem is not well appreciated

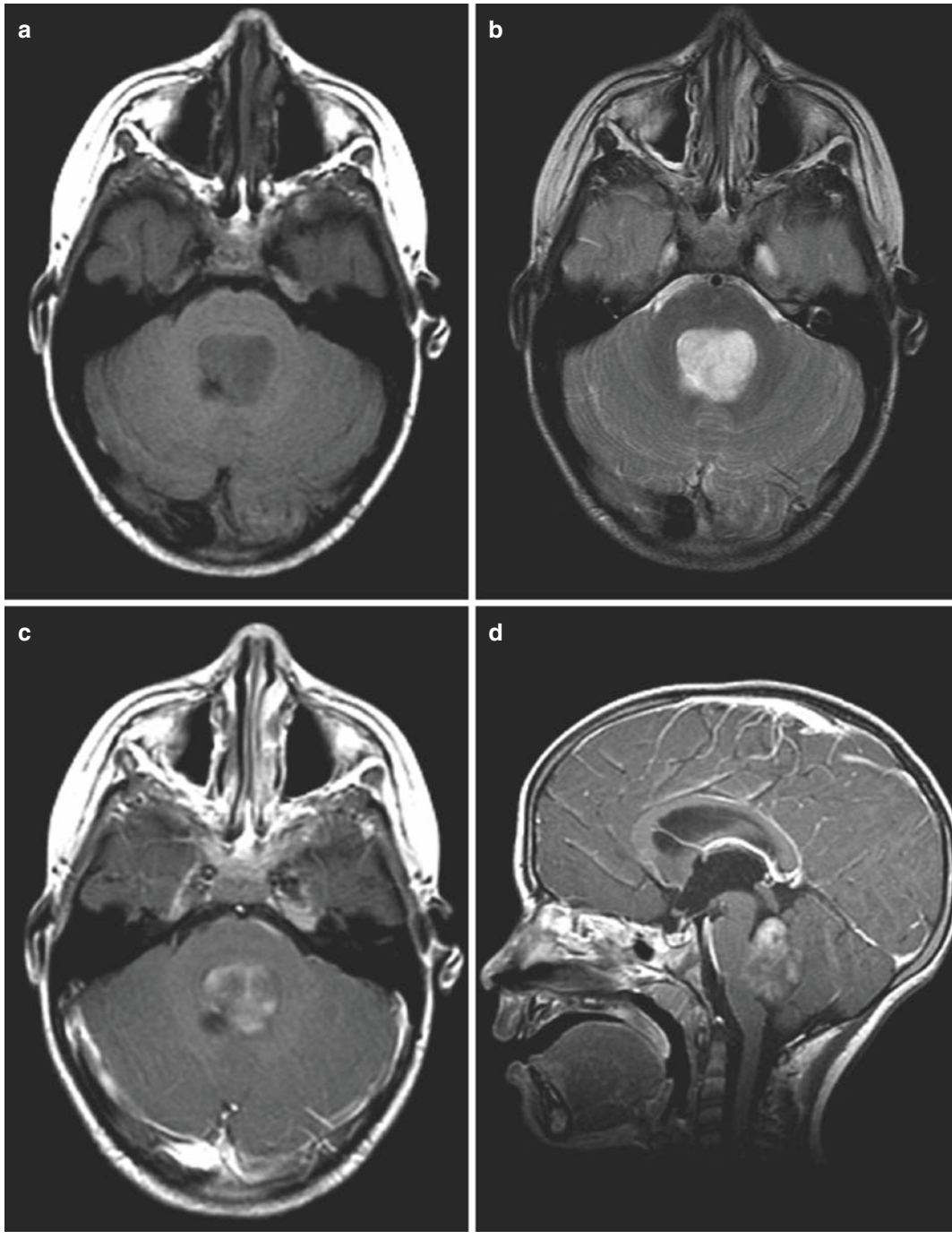

Fig. 20.10 MRI scan of dorsally exophytic brainstem glioma in patient described in Fig. 20.8. (**a**) Axial T1 MRI showing lesion directly opposed with the floor of the fourth ventricle. (**b**) Axial T2 MRI showing high signal intensity lesion in the fourth ventricle. (**c**) Axial T1 MRI with contrast showing somewhat patchy enhancement of the lesion. (**d**) Sagittal T1 MRI with contrast depicting the relationship of the tumor to the floor of the fourth ventricle in better resolution than on CT

toring (IONM), and neuronavigation [7, 24, 25]. Following exposure of the dorsally exophytic mass lesion in the fourth ventricle following standard suboccipital craniotomy and dural opening, tumor is removed stepwise using the ultrasonic aspirator (CUSA), suction, and bipolar cautery (Fig. 20.11). Intraoperative ultrasound is a useful adjunct as well in judging extent of resection, as is intraoperative MRI. Care must be taken not to resect tumor below the estimated plane of the floor of the fourth ventricle. Decisions on where and when to stop neurosurgical resection are aided by feedback from IONM. Postoperative morbidity is usually noted in the form of exacerbation of existing preoperative ataxia, dysmetria, nystagmus, and cranial nerve dysfunction.

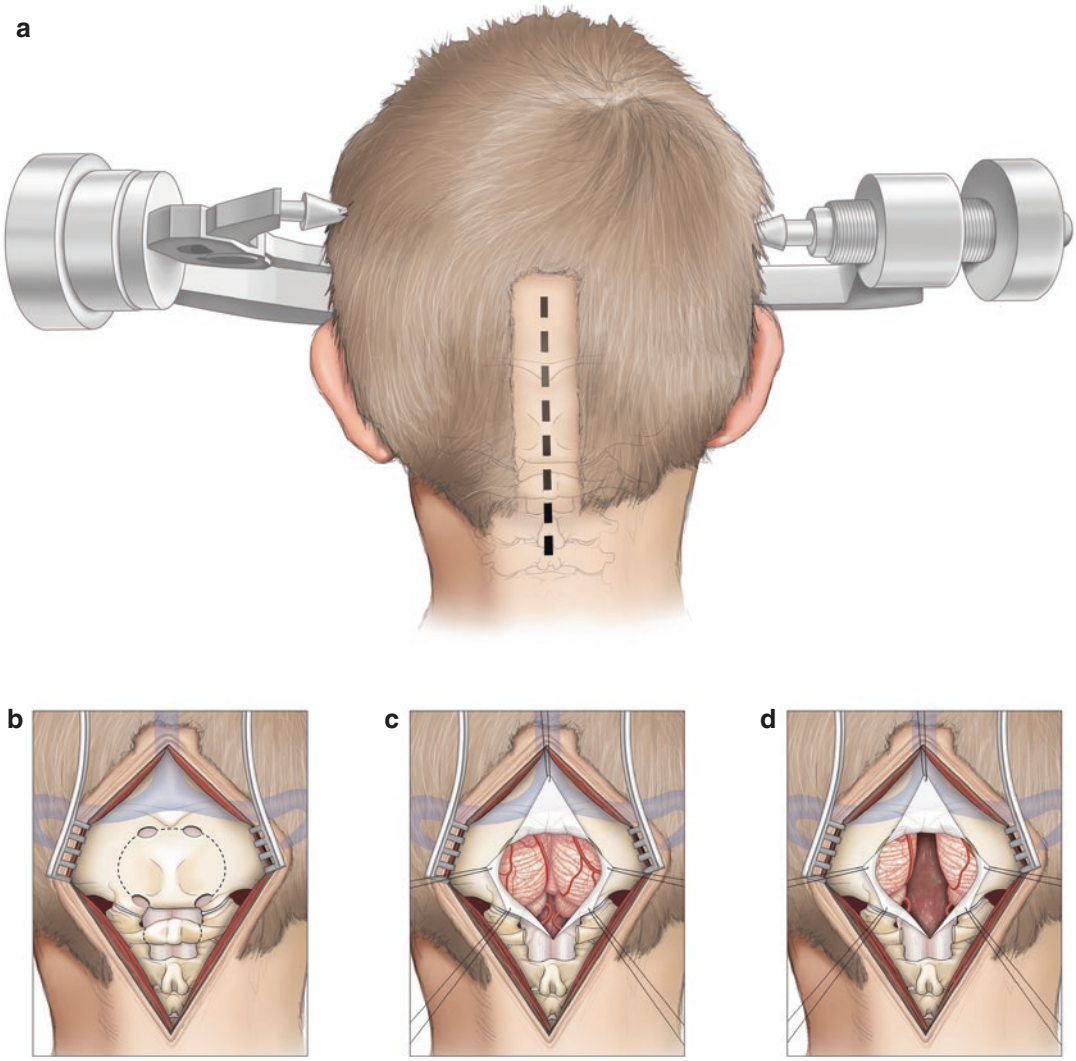

Fig. 20.11 (**a**) Standard midline approach to posterior fossa lesions including dorsally exophytic brainstem glioma. The patient is positioned prone in pin fixation (top image). A small midline hair shave is performed. (**b**) Midline exposure of the occipital region is performed bearing in mind the localization of the transverse sinus on both sides. A craniotomy is performed as shown. Four burr holes are used to prepare the craniotome for bone removal. Care is taken to identify the lip of the foramen magnum so as not to cause a tear in the dura upon using the craniotome. (**c**) The dura is reflected in a Y-shaped manner, and its edges are held back with tack-up sutures. (**d**) The cerebellar hemispheres are gently retracted allowing access to the fourth ventricle. The microscope is used to remove the tumor being careful not to transgress the floor of the fourth ventricle at any time. Alternatively, a telovelar approach can be performed (not shown here)

Radiation therapy may be required for those tumors that have recurred and where further neurosurgical options are limited. Typically, 54 Gy delivered in 30 fractions over 6 weeks is given. Tumor control after radiation therapy has been described as generally favorable in many series [23].

These days, with the known biological targeting of low-grade gliomas in children, dorsally exophytic pontine gliomas may be amenable to chemotherapy. In the past, carboplatin and vincristine have been used. Now, with various BRAF mutations and fusion anomalies discovered, BRAF inhibitor therapy is being explored at this time [26–28].

20.3.2.5 Prognosis/Quality of Life

Overall 5-year survival for the dorsally exophytic pilocytic lesions is good, with rates in most studies of about 95% [23]. Recurrence is recognized even with gross total excision, such that progression-free survival rates at 5 years are between 54 and 72% [23]. Other factors that worsen survival are cranial nerve (particularly abducens) dysfunction at presentation and symptom duration of less than 6 months. Total or subtotal excision of low-grade brainstem lesions has been shown to have an improved outcome compared to partial (<50% of total tumor mass) excision. Long-term neurological function following surgery for dorsally exophytic lesions is generally good, with most patients being either at their presentation baseline or improved.

Although the outcome for the dorsally exophytic pilocytic gliomas is good, the rarer fibrillary gliomas may carry a very poor prognosis. Various novel modalities of treatment are being investigated, including convection-enhanced and slow-flow delivery of chemotherapeutic agents, radiosensitizing agents, gene therapy, and hyperbaric and interstitial radiotherapy. Ultimately, a deeper understanding of the molecular biology of these tumors will lead to improvements in treatment with targeted therapies.

20.3.3 Cervicomedullary Gliomas

20.3.3.1 Symptoms and Clinical Signs

Cervicomedullary gliomas (CMGs) are intramedullary tumors that develop around the craniovertebral junction. They are rare, slow-growing, and histologically benign tumors that typically present with a variety of neurological symptoms including those of lower brainstem dysfunction and those of myelopathy [29]. Patients with tumors located in the medulla typically develop nausea, vomiting, failure to thrive, lower cranial nerve dysfunction, chronic aspiration, sleep apnea, and obstructive hydrocephalus. Tumors located in the upper cervical spine lead to changes in hand preference, gait, and motor regression especially in younger patients. They can also lead to hypo-/hyperreflexia and facial pain. However, independent of anatomical origin, as the tumor expands, patients have a mixture of these signs and symptoms.

20.3.3.2 Diagnostics

Regardless of location, CMGs present with clinical, radiologic, and pathological similarities. MRI is used as an initial diagnostic tool, and tissue diagnosis at the time of surgery leads to the final pathology. On MRI, the majority of CMGs are hypointense to white matter. On T2 and proton density images, they are hyperintense to white matter (Fig. 20.12). On sagittal MRI, CMGs extend from the caudal two thirds of the medulla to the rostral aspect of the cervical cord. They tend to enhance avidly following contrast administration.

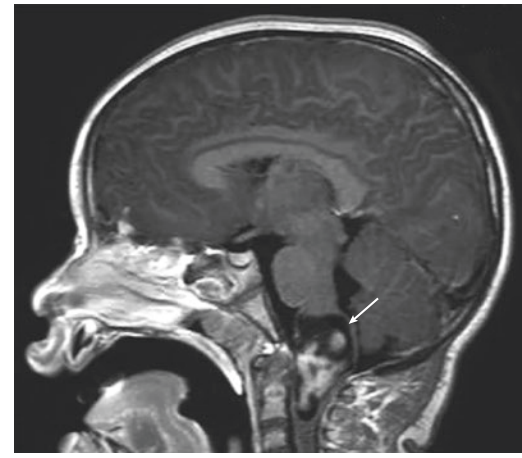

Fig. 20.12 Sagittal MRI of a 6-year-old female showing enhancing lesion of the cervicomedullary junction. This child presented with seizures initially but then went on to display progressive left hemiparesis

CMGs are typically low-grade neoplasms and may be gliomas or gangliogliomas [30]. Occasionally, anaplastic changes may be found in these tumors [29].

20.3.3.3 Classification

There is no standard classification system of CMGs. Since most of these tumors are low-grade, they are inclined to grow circumferentially around pial structures and become redirected at white matter tract interfaces. Thus, the pyramidal decussating fibers and medial lemniscus restrict their spread into the pontomedullary junction and instead direct their growth in the direction of the fourth ventricle. This growth restriction can subsequently lead to well-defined tumor borders and thus easier resection for the surgeon.

20.3.3.4 Treatment

Though conventional treatment for these tumors is by means of surgical resection, there has been a great amount of discussion on the role of radiation and chemotherapy as adjuncts to surgery. The role of surgery is indispensable as it allows the diagnosis to be made via tissue biopsy and decompression of the brainstem and cervical spine, along with treating an associated syrinx or potentially. However, complete resection is often not possible due to poorly defined tumor borders and/or unacceptable risk of neurological deficit. Valuable tools such as ultrasound, intraoperative MRI, stereotaxy, and neurophysiological monitoring are available for achieving maximal resection [7, 24, 25] (Fig. 20.13).

As previously stated, surgery may not be curative in some instances for low-grade lesions and is never curative with high-grade lesions. Radiation therapy (RT) is considered an optional treatment modality for CMGs. It can be used as primary treatment or salvage treatment for low-grade lesions and can be considered in tandem with chemotherapy for primary treatment of

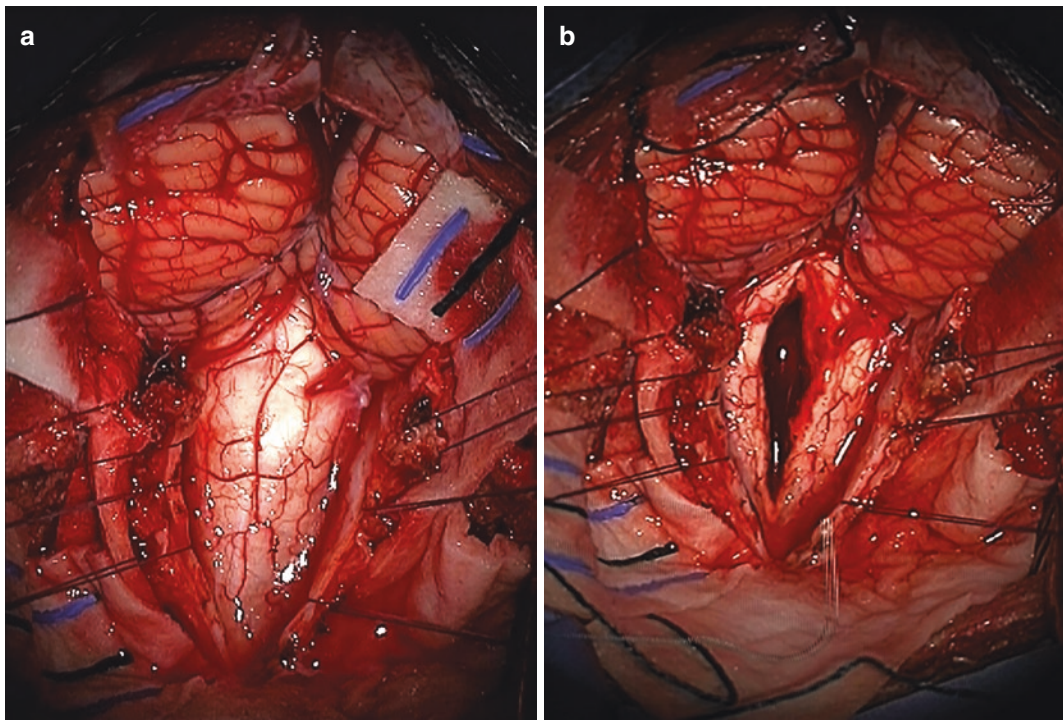

Fig. 20.13 Intraoperative photograph of cervicomedullary glioma in patient described in Fig. 20.11. (**a**) Following posterior fossa craniotomy and cervical laminotomy, the cervicomedullary glioma is seen. A midline myelotomy was made, and the tumor was debulked cautiously under continuous neuromonitoring, using the CUSA. (**b**) Immediate post-resection photography showing midline myelotomy and resection of the cervicomedullary glioma

malignant tumors not amenable to surgical resection. A more conservative surgical approach may be indicated for CMGs that demonstrate enhancing tumor tissue among non-enhancing tissue that is continuous with normal cervical spinal cord and/or medulla and/or a poorly delineated tumor/brainstem interface with an abnormal T1 signal extending beyond the apparent tumor into the brainstem on MRI. When these are present on MRI, it is proposed that chemotherapy and/or RT may be superior treatment modalities and provide better survival and neurological outcomes. Chemotherapy alone is typically not considered a standard therapeutic modality but an adjuvant treatment modality in conjunction with surgery and/or salvage treatment for recurrent or progressive tumor [29].

Interestingly, there is a tremendous research focus on the development of novel, targeted therapies based on the specific molecular signature of these tumors. Key tumor molecular markers/pathways have been elucidated, including activation of the ERK/MAPK pathway and identification of KIAA1549-BRAF gene fusions with high frequency [8, 26, 27, 31, 32]. Certain subsets of CMGs are also known to express BRAFV600E mutations. The ERK/MAPK pathway presents a potent area of targeted therapy by MEK inhibitors, which provides a potential alternative treatment modality for patients who are unable to receive maximal resection or do not desire it. Thus, there is tremendous potential for the development of effective targeted therapies as future treatments for CMGs.

20.3.3.5 Prognosis/Quality of Life

CMGs are typically low-grade lesions and thus have favorable overall survival. However, their recurrence rate is high, and they require long-term follow-up to maximize overall survival and neurological preservation. In essence, these tumors take patients down a chronic illness pathway that leads to stepwise deterioration. The goal, of course, is to maximize tumor resection, minimize long-term neurological morbidity, and improve overall quality of life over time.

Interestingly, it has been shown that patients with protracted duration of symptoms prior to diagnosis generally have low-grade tumors with a high probability of long overall survival.

Finally, postoperative cervical sagittal deformity has been reported as a major risk for children undergoing surgery for an intramedullary spinal cord tumor, and this also includes CMGs. At times, instrumented occipito-cervical fusion procedures may be required.

20.4 Conclusions

Brainstem tumors in children are a relatively rare but extremely important subset of brain tumors in children. Their diagnosis is now made fairly accurately on the basis of preoperative MRI scanning which helps apportion these tumors into subgroups affecting the midbrain, pons, and cervicomedullary regions. Despite their critical location, brainstem tumors can now be approached successfully and safely through a number of strategies that have been outlined in this chapter. Tremendous progress has been made in our characterization of the main genetic and epigenetic alterations that affect DIPGs, gangliogliomas, and low-grade gliomas. As a result, there is hope on the horizon that targeted therapy toward activated pathways in these tumors (e.g., BRAF, MAPK, H3KM27, and PDGFB) may provide an additional arm of therapy that will help substantially in improving overall survival and minimizing morbidity in children afflicted with these tumors. In addition, novel drug delivery approaches, such as CED or MRgFUS, should facilitate increased concentrations of targeted therapy into recalcitrant lesions such as DIPG. It is hoped that these approaches will be met with increasing survival advantages among children with these devastating brainstem lesions in particular.

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