Pediatric brainstem tumors

Classifications, investigations, and growth patterns

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ABSTRACT

تمثل الأورام التي تنمو في جذع المخ من 10% إلى 20% من أورام الجهاز العصبي لدى الأطفال. اعتبرت الأورام التي تنمو في جذع المخ في السابق كنسيج مَرضي واحد واستجابتها للعلاج كانت سيئة. خلال الثلاثة عقود السابقة،تقدّم علاج هذه الأورام بشكل ملحوظ نتيجة للتطورات في التقنيات المجهرية وأجهزة التصوير والأهم توفر تصوير الرنين المغناطيسي،في هذه المقالة سوف نستعرض آخر ما توصلت إليه الأبحاث المتعلقة بهذه الأورام وطريقة تشخيصها وتصنيفها وعلاجها. التدخلات الجراحية والتقنيات الحديثة في حال الجراحة لحالات أورام جذع المخ القابلة للتدخل الجراحي سنناقشها في هذه المقالة.

Brainstem gliomas occur in 10-20% of brain tumors in pediatrics. Over the past 3 decades, the treatment of brainstem gliomas has significantly progressed as a result of the gradual advancements in microsurgical techniques, sophisticated imaging technology and, most importantly, the availability of MRI. In this article, we review the current literature on brainstem gliomas and cover diagnosis, imaging, classification, and management. Surgical approaches and intraoperative modalities to tackle operable cases of brainstem gliomas will be discussed in a follow up article.

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The brainstem connects the cerebrum with the spinal cord anatomically. It contains the midbrain, pons, and medulla. It controls life-supporting autonomic functions together with harboring all cranial nerve nuclei along with many other functions. Brainstem gliomas occur in approximately 10-20% of brain tumors in children, with no gender difference, and no race, or geographic predisposition.[1-3] The median age at diagnosis is 6-7 years.[4] In the era preceding modern imaging, all brainstem gliomas were regarded as a solitary pathological entity with poor prognosis. In the late 1960s, Matson[5] suggested that all brainstem tumors were malignant and were deemed inoperable regardless of their histopathological characteristics or location. This assertion was questioned shortly thereafter by Pool,[6] who was one of the first to report tumor resection in the brainstem, which in the case described was inside the aqueduct. In 1980, Hoffman et al[7] described the dorsally exophytic group of brainstem gliomas as a distinct subgroup, and reported that these lesions were surgically curable with aggressive resection. In 1986, Epstein and McCleary[8] described their experience with brainstem gliomas in 34 children. Over the past 3 decades, the treatment of brainstem gliomas has notably progressed as a result of the gradual advancements in microsurgical techniques, sophisticated imaging technology and, most importantly, the availability of MRI. These modalities have revealed that brainstem gliomas are a heterogeneous group of tumors.[8-10]

Neurophysiologic intraoperative monitoring played a key role in further progressing surgeons' abilities to achieve a safer resection.[11,12] Lately neuronavigation, and more recently intraoperative imaging, has positively influenced surgeons to perform safer and more targeted

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surgery.[11] Although various systems are used to classify these tumors (**Table 1**), a classification system introduced by Epstein & McCleary[8] identified brainstem gliomas that benefitted from surgery (**Table 2**). There are 4 types of brainstem gliomas: diffuse, focal, exophytic, and cervicomedullary. The grouping of brainstem tumors according to their manifestation on MRI has been beneficial in expecting their behavior and controlling the management of brainstem tumors. Farmer et al[13] highlighted the fact that several characteristics of these tumors have been identified as favorable prognostic factors, particularly since the introduction of MRI.[13-17] These include tumor focality, growth pattern, gadolinium-enhancement characteristics, and tumor location.[13,16-19] Therefore, MRI can be used to help surgeons identify patients who could benefit from surgery. Overall, 80% of brainstem gliomas occur in the pons and have a poor prognosis, while the remaining 20% that arise from within the midbrain and cervicomedullary have a growth pattern that looks like low-grade glial tumors, and are associated with a better prognosis.[20,21] In this article, we review the current literature on the management of brainstem gliomas, and cover diagnosis and imaging, classification, and

Table 1 - Brainstem tumor classification systems.

Author, year, reference	Imaging modality used for classification	Classification system
Epstein & McCleary, 1986[8]	CT	Intrinsic Diffuse Focal Cervicomedullary Exophytic Anterolateral into cerebellopontine angle Posterolateral into brachium pontis Posterior into the fourth ventricle Disseminated Positive cytology Positive myelography
Epstein & McCleary, 1986[8]	CT, MRI, and surgical observation	Diffuse Focal (less than 2 cm, no edema) Cervicomedullary
Stroink et al, 1987[54]	CT	Group I - dorsal exophytic glioma Group IIa - intrinsic brainstem tumors with hypodensity and no enhancement Group IIb - intrinsic brainstem tumors with hyperdensity and contrast enhancing, exophytic Group III - focal cystic tumor with contrast enhancement Group IV - focal intrinsic isodense with contrast enhancing
Barkovich et al, 1990[15]	MRI	Location (midbrain, pons, medulla) Focality (diffuse or focal) Direction and extent of tumor growth Degree of brainstem enlargement Exophytic growth Hemorrhage or necrosis Evidence of hydrocephalus
Albright, 1996[55]	MRI	Focal Midbrain, pons (dorsal exophytic pontine glioma) Medulla Diffuse
Fischbein et al, 1996[25]	MRI	Midbrain Diffuse, focal, tectal Pons Diffuse, focal Medulla Diffuse, focal, dorsal exophytic
Choux et al, 2000[56]	CT and MRI	Type I - diffuse Type II - intrinsic and focal tumor Type III - exophytic tumor, either dorsally or laterally Type IV - cervicomedullary tumor

Table 2 - Overview and surgical classification of brainstem glioma.

Tumor type	Common clinical presentation	MRI features	Surgery
Diffuse	Multiple CN deficits Long tract symptoms Ataxia	T1 hypointensity T2 hyperintensity Little enhancement	No
Focal	Signs and symptoms of raised ICP, ataxia, isolated CN deficits	T1 hypointensity T2 hyperintensity Variable enhancement	Yes
Dorsally exophytic	Raised ICP from obstructed CSF pathways; failure to thrive, headache, torticollis, prominent nystagmus, and CN dysfunction	T1 hypointensity T2 hyperintensity Bright enhancement	Yes
Cervicomedullary	Lower CN dysfunction, dysphagia, nasal speech, lower tract symptoms, torticollis, and apnea	T1 hypointensity T2 hyperintensity Homogeneous enhancement	Yes

CN - cranial nerve, ICP - intracranial pressure

management. We will discuss the surgical approaches to brainstem glioma in a follow up article.

Imaging and classification. The MRI has improved the understanding and diagnosis of brainstem gliomas because many of these lesions are iso-dense on CT scanning.[22,23] In addition to the clinical picture, an MRI can reveal clues regarding the microscopic pathology of the tumor with a relatively high degree of accuracy. The MRI provides multi-planer images that aid in the diagnosis of tumors, identification of the tumor epicenter, and prediction of its biological behavior.[22,23] Mauffrey et al[19] reported significant differences between the survival curves of patients with non-enhancing lesions and patients with enhancing lesions. The survival rate of patients whose tumors demonstrate gadolinium enhancement on MRI scans was 90% at 2 years, and 40% at 2 years in patients with non-enhancing tumors.[19] Therefore, the value of contrast enhancement in the follow up of patients is essential because increased contrast enhancement may indicate tumor progression.[24] One must take into consideration that high-grade tumors in the pons may have enhancing parts.[25] On the other hand, other diffuse pontine tumors may eventually enhance with time as the tumor progresses and blood-brain barriers are breached and those have a dismal prognosis.[26] Astrocytomas are the most common intrinsic tumor of the brainstem.[27] Histologically, 80% of brainstem astrocytomas are fibrillary in nature and 20% are pilocytic.[27] Other rare tumors originating in the brainstem include subependymomas, gangliomas, and oligodendrogliomas.[25] The magnetic resonance spectroscopy measurement of tumor-associated choline and N-acetylaspartate levels may help distinguish high-grade from low-grade brainstem gliomas.[28] Other new imaging techniques that are used in non-tissue-based diagnoses for brainstem tumors include rapid diffusion MRI, thallium single-photon emission computed tomography (SPECT), and positron emission tomography (PET).[29,30] With the development of diagnostic modalities, significant advances have been made in the classification of brainstem tumors.[9,31]

Diffuse brainstem gliomas. Diffuse brainstem gliomas are the most common tumors of the brainstem, comprising 60-75% of all brainstem tumors.[3,31,32] Most diffuse gliomas involve a large area of the brainstem: the pons and the midbrain, or the medulla oblongata (**Figure 1**).[3] The tumor may engulf the basilar artery in some cases. Diffuse brainstem gliomas are infiltrative, high-grade gliomas appearing hypointense with indistinct margins on T1-weighted MRI scan.[23] They are generally greater than 2 cm in size at the time of presentation.[3] The epicenter of the lesion is usually the pons. Calcium is rarely identified within the tumor. Diffuse gliomas are distinguished from focal tumors by their hyperintensity on T2-weighted MRI images and are associated with significant edema. Diffuse gliomas do not enhance significantly with gadolinium, but may exhibit heterogeneous enhancement with no significant difference in prognosis with or without contrast enhancement.[33] Dissemination along the CSF pathways occurs in around 15% of cases, and therefore imaging the entire CNS axis is very important.[13]

Focal tumors. Focal brainstem gliomas are typically well-circumscribed lesions arising from the midbrain, pons, or medulla (**Figures 2 & 3**).[13,15,34] These are discrete tumors, less than 2 cm in diameter without evidence

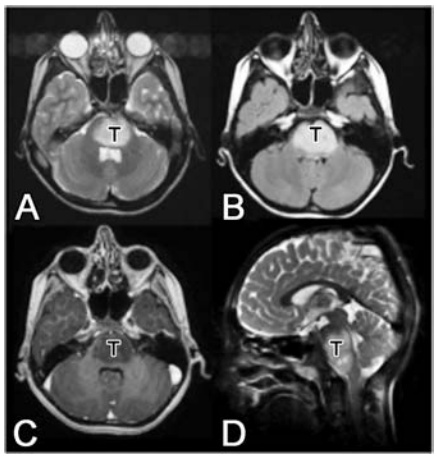

Figure 1 - Diffuse pontine glioma (T) showing **A**) Axial T2 weighted MRI showing a diffusely hyperintense signal in the pons. **B**) Axial flair image at the same cut showing the somewhat more pronounced representation of the same hyperintense area in the pons. **C**) T1 weighted axial MRI with contrast at the same level showing a heterogenously hypointense area of the pons with almost no contrast enhancement seen. **D**) T2 weighted sagittal cuts showing the diffuse pontine glioma occupying most of the pons.

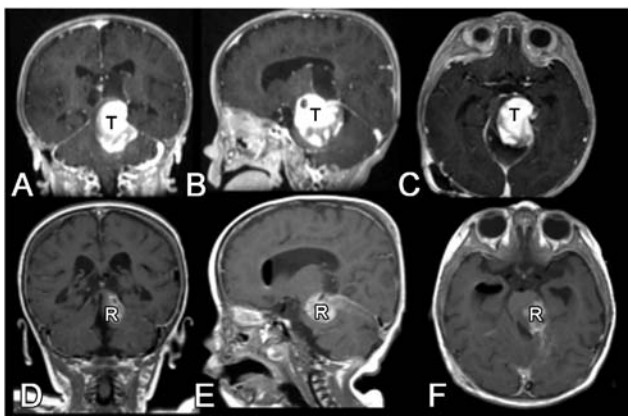

Figure 2 - Dorsal focal-midbrain glioma (T) in a 9-month-old child. **A**) Coronal, **B**) sagittal, and **C**) axial T1-weighted MRI with contrast prior to surgery. **D**) Coronal, **E**) sagittal, and **F**) axial corresponding images after subtotal resection. Residual (R) was treated with chemotherapy.

of locally invasive growth or edema. Focal brainstem gliomas may be further characterized as cystic or solid. The tumors usually demonstrate a hypo or iso-intense signal on T1-weighted MRI and high signal intensity on T2-weighted MRI.[15] Tectal gliomas do not enhance most of the time, and may appear calcified on CT scan. However, peritectal and tegmental tumors more frequently demonstrate enhancement.[35] These focal tumors are mostly benign, grade I (pilocytic), or grade II astrocytomas.

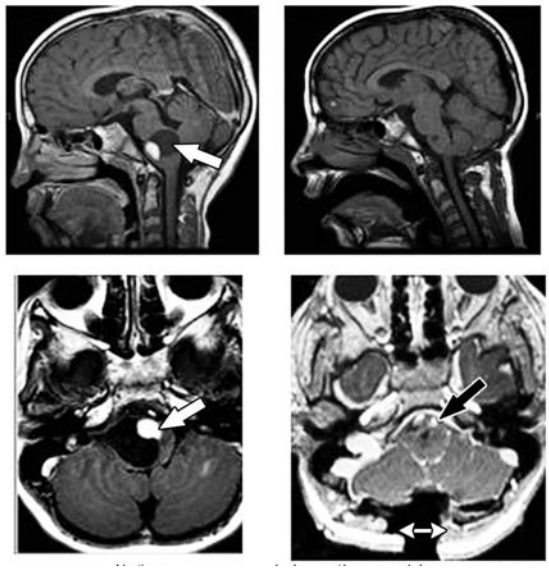

Figure 3 - Focal medullary glioma (white arrows) in a 9-year-old child. Sagittal (top) and axial (bottom) T1-weighted contrast enhanced images before (left) and after (right) complete resection and return of vertebral arteries to normal position (black arrow) as seen in an intraoperative MRI (skin is still open, double arrow).

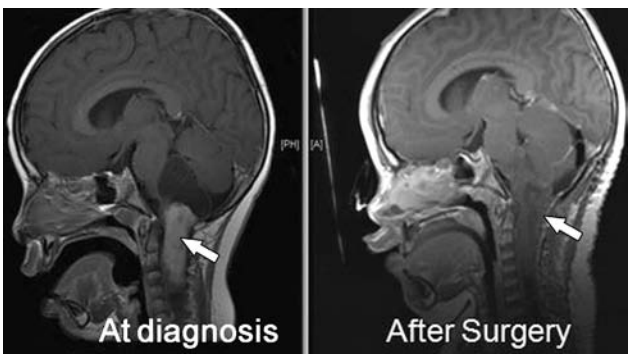

Figure 4 - Cervicomedullary glioma (arrow), before (left) and after (right) surgery.

Exophytic tumors. Hoffmann et al[7] was the first to describe this subgroup of tumors. Dorsal exophytic brainstem gliomas are a group of tumors that arise from the subependymal glial tissue of the forth-ventricular floor and fungate into the fourth ventricle.[7] The bulk of the tumor usually grows within the fourth ventricle, which accounts for the relatively late onset of symptoms.[36,37] The clinical history is usually long, with children presenting with vomiting, failure to thrive, and symptoms of increased intracranial pressure if the CSF pathways are obstructed.[37,38] Histologically, these tumors often appear to be low-grade gliomas, and tend to grow along paths of least resistance, namely, into the fourth ventricle and into the cisterns, rather than infiltrate the brainstem.[38] Exophytic tumors that

grow laterally and ventrally into the brainstem are higher-grade tumors compared with exophytic tumors that grow dorsally into the fourth ventricle. They are hypointense on T1-weighted MRI, and hyperintense on T2-weighted MRI. Most exophytic tumors demonstrate homogeneous gadolinium-enhancement.[25,39] Most have been shown to be predominantly pilocytic astrocytomas (grade 1), and grade 2 astrocytomas.[40]

Cervicomedullary tumors. Cervicomedullary brainstem gliomas are tumors that involve the cervical cord and medulla, and are similar to intramedullary spinal cord gliomas (**Figure 4**). They arise either from within the upper cervical spinal cord and grow rostrally, or from within the cervicomedullary junction.[36] On MRI, these tumors show mixed low- and intermediate-signal densities within the solid part of the tumor.[41] An MRI helps in defining the cranial and caudal parts of the tumor. On T1-weighted MRI, most cervicomedullary gliomas are hypointense to white matter. On T2-weighted and proton density images, the lesions tend to be hyperintense to white matter. After gadolinium administration, most lesions demonstrate homogeneous enhancement.[41-44] The pathology is most often that of a low-grade glioma.[42] Only a minority of patients will show a high-grade glioma in this location.

Growth pattern of brainstem gliomas. Rubin et al[9] demonstrated that focal midbrain tumors often remain circumscribed within the dorsal area of the midbrain. Epstein and Farmer[38] demonstrated that diffuse pontine gliomas grow both rostrally and caudally without involving the fourth ventricle. Instead of expanding posteriorly toward the obex, they expand along the medullary axis.[38] Unlike exophytic tumors, because of their infiltrative capacity, the expansion of diffuse gliomas is not diverted by dense fiber tracts of the pons and is not confined by surrounding tissues or anatomic barriers and do not grow in the path of least resistance.[38] Tumors that arise from within the medulla are confined by decussating fibres and expand within the medulla, thereby pushing tracts and nuclei peripherally. Cervicomedullary tumors originate from within the upper cervical spinal cord below the cervicomedullary barrier. Caudal growth is limited by the circumferential pia of the upper cord medulla and follows a cylindrically shaped path. Rostrally, the growth of cervicomedullary tumors is limited by the decussating white matter tracts of the medulla, namely, of the corticospinal tract and medial lemniscus, which act as barriers to tumors growing rostrally from the cervical spinal cord.[38] Because of this barrier, tumor growth is directed dorsally toward the obex of the fourth ventricle where the lesion may rupture into the fourth ventricle.[38]

Diagnosis and management. Clinical history and presentation are important in establishing tumor histology and prognosis.[45] Symptoms at onset may include lower cranial nerve (CN) deficits, long pyramidal tract deficits. and cerebellar signs. Surgery is only potentially beneficial for low-grade focal gliomas, especially if the tumor is located at the cervicomedullary junction.[42] They can have radical surgery with a good outcome and prognosis.[42,43] On the other hand, diffuse gliomas carry a very poor prognosis and surgery is not indicated.[44] Instead, standard treatment consists of conventional fractionated radiotherapy, which may dramatically improve neurological signs, in addition to CSF diversion procedures such as shunting, when tumors obstruct CSF passages; however, the response is short-lived and death typically occurs within 12 months.[44] Chemotherapy has not resulted in improved disease survival.[46,47] The time to diagnosis is an indicator of overall prognosis. Biopsy should play a very limited role in the diagnosis, and should be reserved for lesions with ambiguous MRI findings accompanied by unusual presentations.[48] Brainstem tumors located in the upper region tend to manifest with hydrocephalus.[35] Most midbrain tumors are low-grade that present with obstructive hydrocephalus that results from compression of the aqueduct of Sylvius.[35] Therefore, conservative therapy has been widely advocated for tectal gliomas with third ventriculostomy to relieve the symptoms of increased intracranial pressure.[49] On the other hand, pontine gliomas generally have a poorer prognosis.[4] These lesions usually cause CNS dysfunction (particularly CN VI and CN VII), long tract signs, and ataxia.[3] Lower CN dysfunction, dysphagia, lower tract symptoms, nasal speech, head tilt, palate deviation, and apnea are the main presenting symptoms of cervicomedullary tumors.[42,50,51] Dorsally exophytic tumor symptoms include failure to thrive, headache, vomiting, and ataxia, and are usually managed with subtotal resection and CSF diversion if need.[52,53] In our experience, it is possible to carry out a near total resection in these cases but with the help and guidance of neuronavigation, intraoperative neurophysiologic monitoring, and when possible, intraoperative MRI. These matters, and more will be discussed in an upcoming review article.

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