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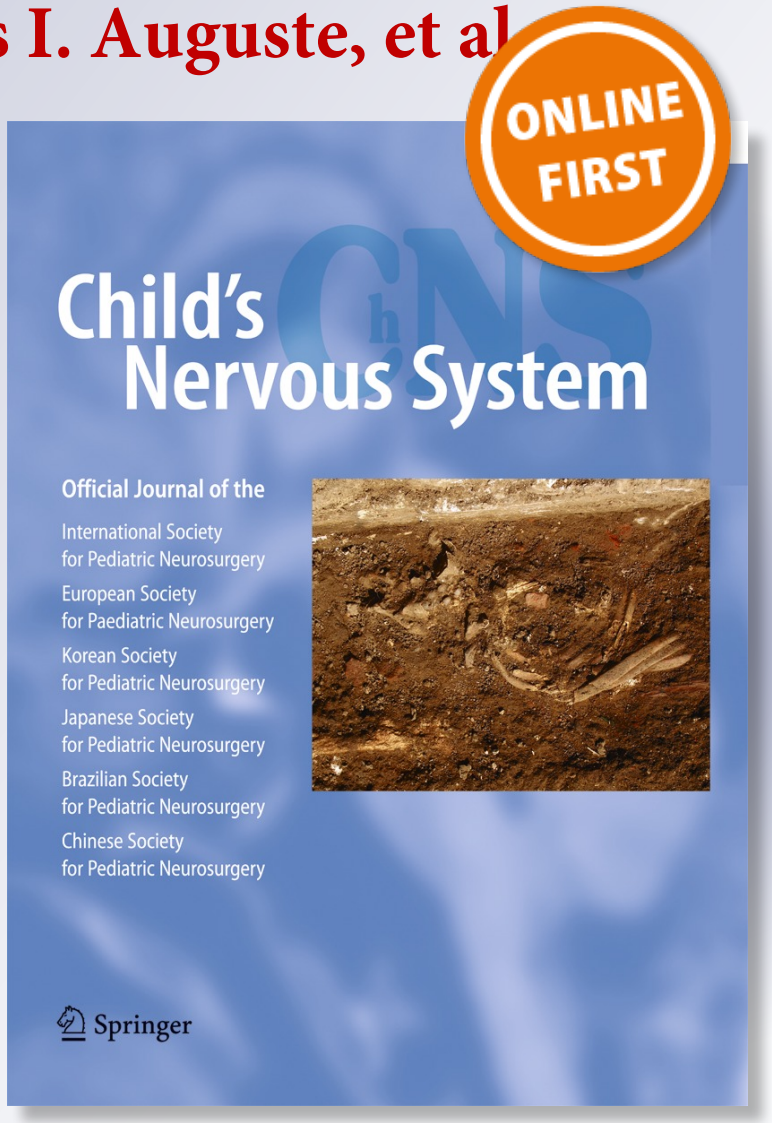

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ORIGINAL PAPER

Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children

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Abstract
Purpose Diffuse intrinsic pontine gliomas (DIPGs) are rapidly progressive and aggressive tumors that usually arise in children. Their anatomic location makes gross total surgical resection impossible, and fewer than 10 % of patients survive more than 2 years after diagnosis. Often, these lesions are treated based on imaging characteristics alone. However, despite aggressive chemotherapy and radiation treatments available, prognosis remains poor. There is therefore a need for new therapies directed by biologic profiling. This necessitates a tissue diagnosis and, therefore, surgical biopsy. We have reviewed the results of biopsy for DIPGs in children at a single institution and compared our results to those available in the literature to elucidate the utility of biopsy for DIPGs.

Methods A historical cohort study was performed using medical records of patients under the age of 18 who underwent surgical biopsy of a DIPG at a single institution.
Results Nine patients were included, four males and five females. Age at presentation ranged from 8 months to 10 years (average 5.7 years). Pathologic diagnoses included five high grade (WHO grade III or IV) gliomas and four low grade (WHO grade II) astrocytomas. There were no intraoperative complications, and only one patient developed a new postoperative neurologic deficit.
Conclusions Stereotactic biopsy of DIPGs is essential to obtain a pathologic diagnosis and is associated with low morbidity. This technique is important to elucidate biological characteristics of these tumors in order to direct multidisciplinary treatment plans possibly involving chemotherapy, radiation therapy, or other future clinical trial interventions for children with DIPGs.

Keywords Pediatric · Brainstem tumor · Biopsy · DIPG

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Introduction

Brainstem gliomas account for 10–15 % of primary brain tumors in children [1]. Males and females are equally affected, and the mean age at initial diagnosis is between 7 and 9 years [2, 3]. Tumors of the brainstem demonstrate a striking relationship between location and histopathology. Gliomas arising at either pole of the brainstem, in the midbrain and medulla, are usually WHO grade I tumors, while the majority of tumors arising in the pons have a diffusely infiltrative character and a rapidly progressive natural history. The name, diffuse intrinsic pontine glioma (DIPG), defines their origin in the brainstem

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and the infiltrative character; both features that preclude surgical resection. The imaging appearance of DIPGs is characterized with homogeneous enlargement of the pons most clearly visible on T2-weighted sequences. Unlike virtually all other primary brain tumors, the MR imaging features of DIPGs are felt to be sufficiently specific that surgical biopsy has not been performed routinely [4]. This situation is unlike virtually any other location in the brain where obtaining tissue is the first step prior to the initiation of appropriate chemotherapy or radiation therapy.

The prognosis for patients with DIPGs is extremely poor, and fewer than 10 % of patients survive longer than 2 years after initiation of radiation and/or chemotherapy treatment [1]. Many clinical trials investigating a broad range of chemotherapeutic options in the past 20 years have been used for DIPGs, and none have led to an increase in survival [5, 6]. Until very recently, the biology of DIPGs was entirely unknown, but analysis of postmortem tissues and some surgical biopsies has suggested that identifiable genetic and molecular alterations exist in these tumors that may serve as therapeutic targets [7–9]. Early pathologic profiling of these tumors has indicated that pediatric DIPGs are genetically distinct from adult gliomas. Markers such as EGFR and IDH-1 that have been identified in adult tumors have not been found in their pediatric counterparts [7, 10]. Similarly, some pediatric DIPGs express PDGFRA, RB, or MET amplifications which are not common in adult gliomas [7, 8].

There is a perception that surgical biopsy of intrinsic brainstem tumors carries an excessive risk that precludes its use. Although the brainstem is an eloquent location, there has been a number of case series over the past several years that have reported surgical morbidity associated with procedures in this area [11–13]. The aim of this study was to retrospectively review the experience at a single institution of surgical biopsies of primary neoplasms involving the pons in children and to place those results in the context of those available in the literature. We conclude that surgical biopsy can be performed in this location with acceptable morbidity and mortality, and should be considered for patients who meet the appropriate clinical criteria, or when participating in an approved clinical research study in an effort to gain genetic information from these tumors to direct future therapies.

Methods

Subject population

We retrospectively reviewed medical records of all patients under the age of 18 who underwent biopsy or open surgical resection for intrinsic brainstem tumors at the University of California, San Francisco from 2000 to 2011 under an approved Committee for Human Research protocol. Tumors arising from the cerebellum or cerebral hemispheres were excluded, as were dorsally exophytic tumors of the pons, well-defined lesions involving the tectum of the midbrain, and tumors arising from elsewhere in the brainstem. Nine patients met the inclusion criteria for this study. Inpatient and outpatient records were reviewed to gather demographic information, presenting symptoms, radiographic images and reports, pathologic diagnoses, operative technique, treatment choices, and clinical outcomes. We paid special attention to any postoperative neurologic deficits experienced either transiently or permanently following stereotactic biopsy.

Surgical technique

All patients underwent stereotactic biopsies. Preoperatively, patients all completed an MRI with and without gadolinium intravenous contrast of the brain according to Brainlab (Brainlab AG, Germany) protocols to allow for intraoperative neuronavigation. Patients were positioned either supine ($n=3$) or in the lateral decubitus position ($n=6$) opposite the side of their lesion with neck flexion in the same direction. The head was then fixed using both a horseshoe head holding device and further immobilized with Mayfield pin fixation. For all stereotactic procedures, the Brainlab neuronavigation system was used to plan the trajectory from the skull to target locations in the brainstem. The biopsy entry point was transcerebellar, either right ($n=4$) or left ($n=5$) for all patients. A side-cutting biopsy needle was then passed along the trajectory path. Between one and four samples were obtained from within the lesion.

Target selection

In all cases, the tumor involved the pons and was not amenable to resection or debulking. All tumors had typical imaging features consistent with a DIPG. For these tumors, the border of the tumor usually approached the middle cerebellar peduncle on one or both sides. Target selection was designed to minimize the trajectory through the brainstem. If there was an obvious area of enhancement suggesting a pathologically aggressive area of the tumor, then this was chosen as the biopsy target. Otherwise, the target was usually just deep to the cerebellar peduncle. Care was taken to avoid the lateral edge of the fourth ventricle and the ventral corticospinal tracts. In later cases ($n=3$),

diffusion tensor imaging (DTI) was used to identify the location of the corticospinal tracts (Fig. 1). Target sites in the ventral portion of the pontine tegmentum were avoided.

Results

Patient population

Roughly, equal number of males (n=4) and females (n=5) were included (Table 1). The average age at presentation and therefore at surgical diagnosis was 5.7 years, range (8 months to 10 years). Patients included in this study presented with a variety of symptoms (Table 2). The most common presenting symptoms were cranial neuropathies experienced by seven out of nine patients, followed by ataxia or falls (five patients), and headache in three patients.

Tumors arose from the pons, and in some patients were so expansile and diffuse that they spread to involve surrounding brainstem structures, and in one case even the cerebellum (Table 1). Imaging features were consistent with DIPG. Five tumors were diagnosed pathologically as high grade glioma, either WHO grade III anaplastic astrocytoma or WHO grade IV glioblastoma. The remaining four were low grade WHO grade II astrocytomas. The majority of patients (n=7) underwent chemotherapy and radiation therapy following diagnosis, the remaining two patients underwent biopsy plus chemotherapy alone.

Surgical morbidity

All procedures were performed without any intraoperative complications. Specifically, no episodes of bradycardia or hemodynamic instability were observed. Only one patient had new postoperative neurologic deficits. This patient developed seizures and hydrocephalus that were treated with ventriculoperitoneal shunt. The remaining eight patients had no new postsurgical deficits. However, they all went on to experience the natural history of their disease despite adjuvant therapy and had associated decline in neurologic exam as well as functional status. At this time, four patients have died from the progression of their disease, two with high grade gliomas (survival time of 12 months), and the others with low grade tumors (survival time of 6 and 11 months).

Discussion

For virtually all other primary tumors arising in the CNS, the first treatment step is either surgical resection or biopsy. Subsequent therapeutic decisions are primarily influenced by the

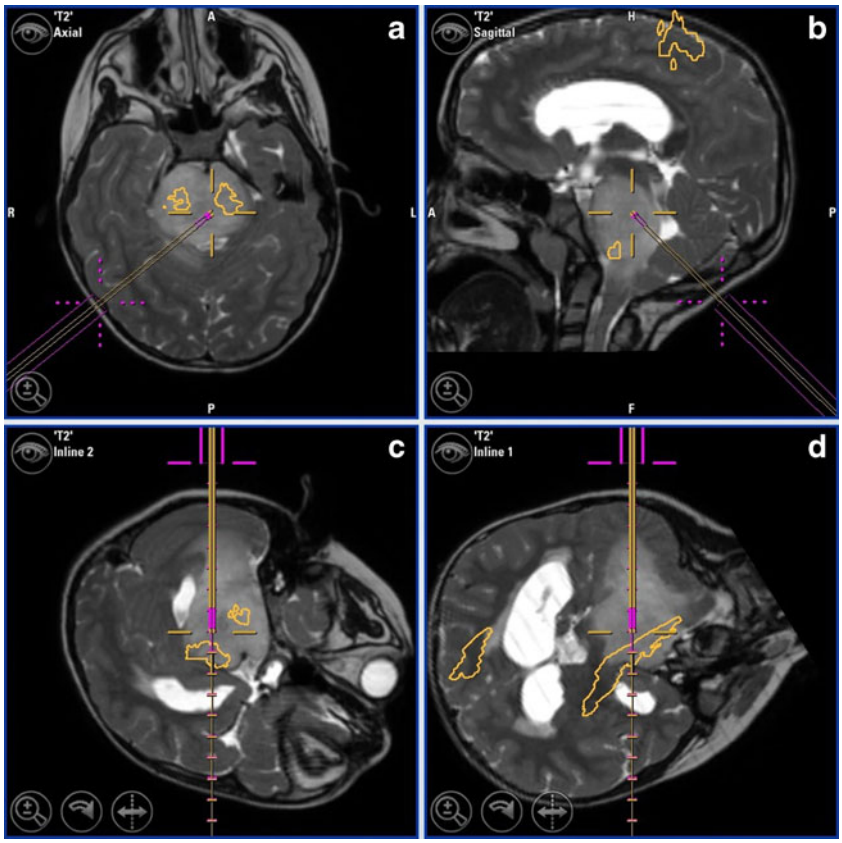

Fig. 1 A screen capture from a stereotactic biopsy of a patient with a DIPG. The T2-weighted images demonstrate axial (*top left panel*), sagittal (*top right panel*), and trajectory views (*bottom panels*) at the time of biopsy. The descending corticospinal tracts were identified using DTI and superimposed on the neuronavigation image set. The trajectory selected was chosen to avoid the corticospinal tracts

Table 1 Patient profile and biopsy outcome

Patient no.	Age (yr) at dx	Sex	Tumor location	Tumor size	Pathology	Biopsy route	Surgical approach	No. of surgical passes	Postoperative deficits
1	9	M	Pons	–	WHO IV GBM	TC	R occipital burr hole	4	None
2	1	M	Pons	3.8×4.4×4.1 cm	WHO III astrocytoma	TC	L occipital bur hole	2	None
3	10	F	Pons	4.5×5.1×4.4 cm	WHO II astrocytoma	TC	L posterior fossa bur hole	3	None
4	5	F	Pons, midbrain	4.0×5.5×5.0 cm	WHO II astrocytoma	TC	L posterior fossa bur hole	1	None
5	8mo	M	Medulla, pons	0.9×2.3×2.4 cm	WHO II astrocytoma	TC	L occipital bur hole	2	None
6	9	F	Pons	3.7×2.3×2.7 cm	malignant glioma	TC	R occipital bur hole	2	None
7	6	F	Pons, midbrain, R cerebellar peduncle, R cerebellum	4.2×4.8×4.4 cm	WHO III astrocytoma	TC	R occipital bur hole	>1	None
8	4	M	Pons to spinal cord	5.8×3.8×5.9 cm	WHO III astrocytoma	TC	R posterior fossa bur hole	>1	None
9	3	F	Pons, medulla	5.0×4.2 cm	WHO IV GBM	TC	L occipital bur hole	>1	Seizures, hydrocephalus s/p VPS

TC transcerebellar, *VPS* ventriculoperitoneal shunt

pathologic diagnosis and/or grade of the tumor. Tumors of the brainstem are an exception to this paradigm, mainly because of the unusual correlation between location and pathology. Well-defined tumors of the tectal plate are usually WHO grade I neoplasms that commonly present with obstructive hydrocephalus. Direct treatment of the tectal mass is rarely required [14]. At the opposite pole of the brainstem, tumors of the medulla are usually WHO grade I pilocytic astrocytomas whose relationship to the medulla usually allows either total or subtotal resection [15]. In contrast, DIPGs that arise in the pontine tegmentum are associated with a typical imaging appearance that often provides sufficient confidence to start treatment without pathologic confirmation.

Although many experimental agents have been tested over the past two decades, there is little evidence that any improvement in survival occurs beyond standard treatment, which is fractionated external beam radiotherapy. This lack of progress has led to a degree of therapeutic nihilism regarding the treatment of these patients. There is some hope, however, that the use of targeted biologic agents will spur a new approach to the treatment of DIPGs and other challenging tumors. However, the use of these agents in future phase I and II clinical trials will certainly require tissue in order to determine a molecular phenotype prior to treatment assignment, measure response of a targeted biochemical pathway, or determine molecular changes at recurrence. Some biologic markers that are being investigated include PDGFR alpha, EGFR, and IDH-1 mutations. In addition, unequivocally diagnosing DIPG based solely on radiographic imaging prior to initiating treatment has been a source of debate. This inconsistency in the field again stresses the importance of obtaining a tissue diagnosis. For these reasons, we wished to define the surgical morbidity associated with procedures performed upon tumors in this location as compared to results reported by other groups.

Table 2 Clinical findings at presentation

Clinical symptom	No. of patients
Cranial neuropathy	7
Ataxia/dysmetria/falls	5
Headache	3
Hemiparesis/clumsiness	2
Nausea/constitutional symptoms	1
Hydrocephalus	1
Head tilt	1
Respiratory distress	1

From a technical perspective, it is important to avoid white matter tracts that pass through the brainstem and cranial nerve nuclei within the pons. There are specific imaging tools that will help to achieve this objective. DTI and white matter tractography are useful in determining the location of the corticospinal tracts [16]. For DIPGs, these tracts are usually infiltrated by the tumor but are located in the anterior pontine tegmentum. A surgical entry point over the lateral cerebellar hemisphere will avoid passing

through the corticospinal tracts and the more medially located deep cranial nerve nuclei (Fig. 1). Other groups have reported the use of PET to define the lesion [17]. By targeting PET "hotspot(s)" on the first biopsy pass, the number of passes with the biopsy needle may be reduced, thereby lowering morbidity [11].

Our own clinical experience suggests that stereotactic biopsy of pontine tumors in children is technically straightforward and carries a low morbidity. Although a transcerebellar approach was used to access the lesions described in this series, a transfrontal route is also acceptable for some intrinsic pontine lesions. Only one out of nine patients had a postoperative complication consisted of seizures and hydrocephalus and were not directly related to the procedure. No patients died as a direct result of the procedure. Other case series have also reported results after surgical biopsy of brainstem tumors (Table 3) [12, 18–36]. Some of these studies include adult and pediatric patients, and some also included tumors that were treated by open surgical resection. For those reports in which patient ages were available, an excess of 300 pediatric patients had surgical biopsies. Among this entire group, adults and children, new symptoms were relatively infrequent, and the majority of these consisted of transient cranial neuropathies or mild motor weakness.

Our results and those from other studies raise the question of which clinical indications should prompt a surgical procedure for brainstem tumors. Certainly, for tumors that are surgically resectable (e.g., dorsally exophytic tumors, cervicomedullary tumors that reach the pial surface), an open craniotomy and attempt at resection is warranted. In a cohort of adult patients with brainstem masses, Sanai et al. found that the expected diagnosis differed from the actual diagnosis in 9 of 13 cases [27]. In children, pontine tumors that do not have a typical imaging appearance of a DIPG should have pathologic confirmation to exclude a diagnosis that would require substantially different treatment (e.g., lymphoma, PNET). It should be noted that in one series of 44 patients with diffuse lesions, 10 % had a pathologic diagnosis different from glioma [13].

What about tumors that have the typical imaging appearance of a DIPG? At present, it is still acceptable to initiate standard therapy (fractionated external beam radiotherapy) without pathologic confirmation. The cumulative experience summarized in Table 3 suggests that image-guided stereotactic biopsy of intrinsic lesions of the pons can be

Table 3 Summary of case series [12, 18–36]

Authors and year	No. of total cases	No. of pediatric cases	No. of transcerebellar	No. of transfrontal	Intraoperative complications	Postoperative morbidity	Inconclusive biopsy	Deaths
Coffey and Lunsford, 1985	13	1	2	11	0	0	0	0
Giunta et al., 1988	22	13	17	5	2	1	2	0
Mathisen et al., 1987	29	12	29	0	0	2	3	0
Abernathy et al., 1989	26	6	26	0	0	0	0	0
Giunta et al., 1989	35	15	25	10	0	2	0	0
Guthrie et al., 1989	4	2	4	0	0	1	0	0
Lobato and Rivas, 1989	2,645	NR	14	12	0	0	2	0
Kratimenoss et al., 1992	72	15	0	45	0	3	4	0
Rajshekhar and Chandy, 1995	40	52	2	70	0	5	1	0
Kondziolka and Lunsford, 1995	24	NR	8	32	1	1	1	0
Steck and Friedman, 1995	30	5	2	22	0	3	1	1
Valdes-Gorcia et al., 1998	25	30	26	4	0	1	7	1
Massager et al., 2000	50	5	18	12	0	2	0	0
Chico-Ponce de Leon, 2003	50	50	Unknown	Unknown	9	9	1	0
Goncalves-Ferreira et al., 2003	30	3	19	11	3—unable to reach lesion	2	5	0
Pincus et al., 2006	10	10	4	6	0	1	0	0
Roujeau et al., 2007	24	24	24	0	0	2	0	0
Sanai et al., 2008	13	0	13	0	1	1	1	0
Patel and Balamurugan, 2009 (28)	24	24	24	0	0	3	1	0
Perez-Gomez et al., 2010 (31)	20	20	20	0	0	2	0	0
This current series, 2012	9	9	9	0	0	1	0	0

performed safely with at least equal morbidity when compared to biopsy procedures performed in other brain locations. The postoperative complications do not appear to be unexpected or unacceptably high. Indeed, case reports have demonstrated the feasibility of performing therapeutic convection-enhanced delivery to the human brainstem [37]. Another factor is the emerging role of molecular classification of brain tumors. For DIPGs, alterations include amplification of PDGFR alpha, increased expression of EGFR, mutations in H3 histone proteins, TP53, and PI3KCA [38–41]. These early reports have small cohorts of patients, and these results will only be generalizable after the analysis of much larger cohorts of patients. Clinical trials currently being developed for most childhood malignancies will rely heavily on genomic and biologic characterization, which will require surgical biopsy prior to treatment.

The pathologic diagnosis obtained from biopsy in this series provides some clues regarding the molecular pathogenesis of DIPGs. Although most patients usually present with mild or minor symptoms, the initial imaging study invariably shows a widely infiltrated pontine tegmentum. This observation alone suggests that most DIPGs are present for a long time as a slowly infiltrating neoplasm. The development of symptoms probably coincides with the transformation of the preexisting low grade tumor into a malignant genotype, which then leads to rapid mortality. It is likely that this early transformation precedes the development of detectable MRI changes. This possibility is consistent with the WHO grade II histopathology of the tumor specimen that was observed in four patients in this series. Since patients with typical DIPGs demonstrate rapid tumor progression, it is likely that higher grade elements are present within the tumor, but these may precede any imaging changes. The two patients in our series who were diagnosed with WHO grade II tumors at the time of surgery, and yet died 6 and 11 months later from tumor progression, support this possibility. Three biopsy samples were taken from two distinct sites in one patient, and two samples were taken from a single site in the second patient. Mixed pathologic findings were identified in both lesions. One patient demonstrated both grades I and II features at a single biopsy site. Though no mitotic figures, necrosis, nor vascular invasion were identified in the other patient's tumor, the MIB-1 index—a measure of cell proliferation—was high and therefore concerning for high grade features elsewhere in the mass. Although the final pathologic diagnoses met the criteria for a WHO grade II lesion, these other features strongly suggest mixed malignant histologic cell populations coexisting in a single tumor. Indeed, a detailed understanding of the biology of these tumors should provide some hope of improving the outcome of these patients; more so than what has been accomplished in the past two decades. It is this objective that makes the characterization of tumor specimens early in the disease progression particularly important.

Conclusions

Stereotactic biopsy of brainstem tumors in pediatric patients carries a low associated morbidity. By obtaining tissue diagnosis from surgical biopsy, biologically-directed therapy can be selected. Neurosurgeons and neurooncologists should consider surgical biopsy as a reasonable option that can be included as a component of a carefully considered treatment strategy, particularly one that involves patient participation in a clinical trial.

Disclosure The authors report no conflict of interest concerning the materials or methods used in this study of the findings specified in this paper.

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