Abstract
Brainstem tumors are rare pathologies, brainstem glioblastoma is even rarer. We report three pediatric patients who underwent subtotal tumor resection for brainstem tumors diagnosed as brainstem glioblastoma. The clinical courses and treatment procedures were discussed alongside a comprehensive literature review. Treatment of brainstem high-grade gliomas includes steroids, surgery, radiotherapy, and chemotherapy. However, none of these treatment modalities effectively prolongs survival time. According to literature, the median overall survival of these patients are approximately between 9 to 12 months. Glioblastoma has a poor prognosis in pediatric patients with high-grade brainstem gliomas. Radiotherapy is associated with a decreased risk of mortality at 9 months but not long-term.

Keywords: Brainstem, glioblastoma, pediatric, chemotherapy, radiotherapy

Öz

Anahtar Sözcükler: Beşin sapı, glioblastom, pediatrisk, kemoterapi, radyoterapi
**Introduction**

Central nervous system tumors are the most common type of solid cancers in the pediatric period. Averagely 10%–15% of them are located in the brainstem. Brainstem tumors are divided into four classes according to magnetic resonance imaging (MRI) scans. These include diffuse intrinsic (type I), focal (type II), dorsal exophytic (type III), and cervicomedullary (type IV). Diffuse intrinsic brainstem gliomas are the most frequent tumors among brainstem tumors. They constitute approximately 75%–80% of all brainstem tumors. Approximately 30%–40% of these gliomas are brainstem glioblastomas. Surgical excision of these tumors is almost impossible in most cases, and added to their troublesome clinical course due to brainstem compression, the prognosis of brainstem glioblastomas is very poor. In our report, we present three pediatric patients who underwent operation for brainstem tumors diagnosed as glioblastoma from histopathological examination. The clinical course and treatment modalities of this rare pathology were discussed with the backing of comprehensive literature review.

**Illustrative Cases**

**Case 1**

We admitted a 7-year-old girl to the Neurosurgery Department presenting with headache, dizziness, diplopia, and right-sided muscle weakness for six days. Her neurological examination revealed right hemiparesis (muscle strength was 3/5) and lower cranial nerves dysfunction. There was no contributive medical past history. MRI revealed an expansive and cystic pontine mass of $32 \times 26 \times 28$ mm showing peripheral contrast enhancement (Figure 1A). She underwent subtotal tumor resection via left sided suboccipital craniotomy.

Histopathological examination of the tumor revealed small, elongated bipolar atypical cells, proliferated tumor vessels, and ischemic necrosis (Figure 2). Pathological diagnosis was isocitrate dehydrogenase type 1 (IDH)-mutant high-grade glial tumor with a proliferation index of 15%–20%. Postoperative contrast enhanced cerebral MRI scans showed the decrease in tumor size (Figure 1B).

**Table 1.** Data of the patients with brainstem glioblastoma in the present study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Gender</th>
<th>Surgery</th>
<th>Adjuvant treatment</th>
<th>POD</th>
<th>POD treatment</th>
<th>Survival</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 / F</td>
<td>STR</td>
<td>RT + TMZ-N-V</td>
<td>9 months</td>
<td>TMZ + BVZ + IRN</td>
<td>20 months</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>13 / F</td>
<td>STR</td>
<td>RT + TMZ</td>
<td>24 months</td>
<td>Spinal RT + BVZ + IRN</td>
<td>40 months</td>
<td>DOD</td>
</tr>
<tr>
<td>3*</td>
<td>14 / F</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>DOD</td>
</tr>
</tbody>
</table>


* The patient died in three weeks after the surgery and adjuvant treatment could not be started.
Her postoperative course was uneventful and she was discharged five days after. We started temozolomide (75 mg/m$^2$/day) with concommittant radiotherapy (RT) (total dose: 54 Gy). After completion of RT, we administered nimotuzumab (150 mg/m$^2$/day, first and fifteenth days) and vinorelbin (25 mg/m$^2$/day, first and fifteenth days). After two cycles of chemotherapy, right hemiparesis slightly improved, with no additional clinical findings and with partial decrease in the mass was noticed on MRI.

However, after the third cycle, we noticed deterioration in clinical findings and enlargement of the mass on MRI.

Figure 1. (A) Preoperative axial and sagittal contrast enhanced T1-weighted magnetic resonance images of patient 1 revealing an expansile and cystic pontine mass of 32x26x28 mm. The mass lesion is showing peripheral contrast enhancement. (B) Postoperative axial and sagittal contrast enhanced T1-weighted magnetic resonance images revealing the subtotal resection of the tumor and cystic cavity.
We started a protocol constituting of bevacizumab (10 mg/kg/day first and fifteenth days), irinotecan (150 mg/m²; first and fifteenth days) and temozolomide (150 mg/m²/day 1–5 days). We recorded a slight improvement in motor strength of the right upper and lower extremity. However, she finally died because of the progression of brainstem glioblastoma 20 months after the operation (Table 1).

Case 2

We admitted a 13-year-old female at the Neurosurgery Department presenting with headache and left sided muscle weakness for one week. She also had left sided hemiparesis and exaggerated deep tendon reflexes on neurological examination. She had contributive medical past history. She underwent brain MRI that revealed a diffuse infiltrating pontine tumoral lesion that was heterogeneously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. There was heterogeneously diffuse contrast enhancement after gadolinium administration (Figure 3A). Then, she underwent subtotal tumor resection via right sided suboccipital craniotomy. Histopathological examination of the tumor revealed (IDH)-mutant glioblastoma. She was discharged uneventfully.

Figure 2. Peroperative images of patient 1 revealing; (A) the expansile pontine tumor, (B) drainage of the cystic component of the tumor, (C) resection of the solid tumor components and (D) subtotal resection cavity of the tumor. Fifth cranial nerve is intact after the tumor resection (black arrow). (E) Histopathological examination revealed small, elongated bipolar atypical cells, proliferated tumor vessels and (F) ischemic necrosis confirming the pathological diagnosis IDH-mutant type glioblastoma (H&E, 200X magnification).
Moreover, she underwent cranial RT (total dose: 54 Gy) and chemotherapy (temozolomide, 75 mg/m^2/day). Following the oncological treatments, we achieved tumor regression for two years (Figure 3B). However, new tumoral formation in the fourth ventricle and spinal metastases occurred two years later (Figure 3C). We performed all spinal column RT and chemotherapy treatment as bevacimuzab (10 mg/kg/day first and fifteenth days) and irinotecan (150 mg/m^2 first and fifteenth days). She died because of the progression of the brainstem glioblastoma 40 months after the operation (Table 1).

**Case 3**

We admitted a 14-year-old girl at the hospital presenting with a progressive balance disturbance, headache, vomiting, and diplopia for two weeks. Neurological examination revealed horizontal nystagmus, cerebellar ataxia, limitation of eye abduction and neurological deficit of left cranial nerves VI and VII. Cerebellar tests were positive. Strength, sensation, and reflexes in upper and lower extremities were all normal. Brain MRI revealed a lesion in the midline brainstem that enhanced after gadolinium administration. This lesion was heterogeneously hypointense on T1-weighted images, and heterogeneously hyperintense on T2-weighted images (Figure 4). We subsequently performed a microsurgical subtotal resection of the lesion via suboccipital craniotomy. The pathological findings confirmed the diagnosis of glioblastoma. Adapted oncological treatments could not be started because of the postoperative medical condition of the patient. She died three weeks after surgery (Table 1).

**Review**

A thorough review of the literature revealed 19 research that have reported on clinical cases (Table 2). All of them were clinical case series with a total of 482 pediatric patients. Among the multiple articles previously written by the same authors, the most recent and comprehensive ones were included in the present review. All of the research included all kind of brainstem gliomas, not only high-grade brainstem gliomas. Patients’ data including surgery/biopsy types, histopathologic composition of tumors, adjuvant treatment modalities, median progression-free survival (PFS) and overall survival (OS) were analysed (Table 2).

**Discussion**

Glioblastoma is the most common and most lethal primary brain tumor in adults. However, it is rarer in childhood. Glioblastoma constitutes only 3%–7% of all pediatric central nervous system tumors. The brainstem localization of glioblastoma is uncommon. From literature, two studies presenting the pediatric glioblastoma series have found the rates to be very low. In the study by Nikitovic et al., only 20% of pediatric glioblastoma patients had brainstem glioblastoma. In the other studies, brainstem localization was in 12.5% of pediatric glioblastoma patients.

The initial symptom of brainstem glioblastoma is usually headache. Other symptoms are ataxia, dizziness, weakness, nausea-vomitting, hemiparesis, cerebellar symptoms, and symptoms related with cranial nerve deficits. In some patients, hydrocephalus can be detected due to the compression of fourth ventricle.
Figure 3. (A) Preoperative axial magnetic resonance images of patient 2 revealing a diffuse infiltrating pontine tumoral lesion that was heterogeneously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. There was heterogeneously diffuse contrast enhancement after gadolinium administration. (B) Postoperative first year axial magnetic resonance images showing tumor regression. (C) Postoperative second year axial cranial and sagittal spinal magnetic resonance images revealing new tumoral formation in the fourth ventricle and spinal metastases.
Figure 4. (A) Axial, (B) coronal and (D) sagittal contrast enhanced T1-weighted images of patient 3 showing thick irregular enhanced mass lesion located in brainstem and middle cerebral peduncula with adjacent edema and compression at fourth ventricle. (C) Axial T2-weighted image demonstrate heterogeneous hyperintense mass lesion.
Table 2. Main results of published studies about pediatric brainstem gliomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Surgery / Biopsy</th>
<th>Histopathologic composition</th>
<th>Adjuvant treatment</th>
<th>Median PFS</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brosnicer et al.15, 2005</td>
<td>33</td>
<td>Biopsy (3 patients), STR (1 patient)</td>
<td>3 anaplastic astrocytoma, 1 GBM, 29 BNP</td>
<td>RT + TMZ / IRN</td>
<td>8.8 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Korones et al.23, 2008</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>RT + VCR + VP-16</td>
<td>7 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Massimino et al.25, 2008</td>
<td>62</td>
<td>STR – biopsy (30 patients)</td>
<td>6 grade II astrocytoma, 18 anaplastic astrocytoma, 6 GBM, 32 BNP</td>
<td>RT + Cisplatin + VP-16 + ifosfamide + dactinomycin</td>
<td>10 months</td>
<td>13 months</td>
</tr>
<tr>
<td>Sirachainan et al.28, 2008</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ + cis-retinoic acid</td>
<td>10.2 months</td>
<td>13.5 months</td>
</tr>
<tr>
<td>Janssens et al.20, 2009</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>RT only</td>
<td>5 months</td>
<td>8.6 months</td>
</tr>
<tr>
<td>Jalali et al.19, 2010</td>
<td>20</td>
<td>STR (8 patients)</td>
<td>6 low-grade glioma, 2 high-grade glioma, 12 BNP</td>
<td>RT + TMZ</td>
<td>6.9 months</td>
<td>9.15 months</td>
</tr>
<tr>
<td>Kim et al.21, 2010</td>
<td>12</td>
<td>STR (1 patient)</td>
<td>1 GBM, 11 BNP</td>
<td>RT + TMZ + thalidomide</td>
<td>7.2 months</td>
<td>12.7 months</td>
</tr>
<tr>
<td>Sharp et al.27, 2010</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ</td>
<td>5.13 months</td>
<td>9.8 months</td>
</tr>
<tr>
<td>Wolff et al.29, 2010</td>
<td>37</td>
<td>STR (4 patients),</td>
<td>4 grade II astrocytoma, 8 grade III astrocytoma, 4 GBM, 21 BNP</td>
<td>RT + Cisplatin + VP-16 + VCR + ifosfamide</td>
<td>4.8 months</td>
<td>13.6 months</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Biopsy/RT</td>
<td>Grade of Tumor</td>
<td>Additional Treatments</td>
<td>PFS (months)</td>
<td>OS (months)</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Cohen et al. 16, 2011</td>
<td>58</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ</td>
<td>6.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Kivivuori et al. 22, 2011</td>
<td>8</td>
<td>STR (5 patients)</td>
<td>2 grade II glioma, 3 grade III glioma, 3 BNP</td>
<td>RT + Topotecan + thalidomide + celecoxib + VP-16</td>
<td>11</td>
<td>12.5</td>
</tr>
<tr>
<td>Negretti et al. 26, 2011</td>
<td>22</td>
<td>Biopsy (4 patients)</td>
<td>3 grade III astrocytoma, 1 GBM, 18 BNP</td>
<td>RT only</td>
<td>5.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Bailey et al. 12, 2013</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ</td>
<td>5.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Zaky et al. 14, 2013</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ + BVZ + IRN</td>
<td>10.4</td>
<td>14.6</td>
</tr>
<tr>
<td>Massimino et al. 24, 2014</td>
<td>25</td>
<td>Biopsy (4 patients)</td>
<td>2 grade II diffuse astrocytoma, 2 anaplastic astrocytoma, 21 BNP</td>
<td>RT + N + V</td>
<td>8.5</td>
<td>15</td>
</tr>
<tr>
<td>Hummel et al. 18, 2015</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>RT + TMZ + BVZ + IRN</td>
<td>8.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Rizzo et al. 13, 2015</td>
<td>15</td>
<td>STR (5 patients)</td>
<td>3 anaplastic astrocytoma, 2 GBM, 10 BNP</td>
<td>RT + TMZ</td>
<td>7.15</td>
<td>15.6</td>
</tr>
<tr>
<td>Fleischhacker et al. 17, 2019</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>RT + N</td>
<td>5.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Kebudi et al. 11, 2019</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
<td>RT + N + TMZ / V</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

MRI findings are non-specific and differentiation from other lesions may be difficult. However, features such as heterogeneous signal intensity, prominent heterogeneity and multicentricity associated with a disproportionally large tumor may be useful clues in diagnosing glioblastoma in that location\textsuperscript{1,5}.

Various pathologies with an affinity for the posterior fossa parenchyma may share similar features. Neoplastic diseases (especially pontine gliomas and inflammatory demyelinating lesions) may have similar MRI features. Definitive diagnosis requires histopathological confirmation\textsuperscript{5,6,8}. Klimo et al.\textsuperscript{9} involved 11 patients (38%) having glioblastoma in 29 pediatric patients with malignant brainstem tumors. In their cohort, histopathological diagnoses were identified by stereotactic biopsy in 10 patients, open biopsy in six patients, subtotal resection in eight patients, and gross total resection in three patients. They concluded that maximal resection has favorable effects on long-term survival\textsuperscript{9}. Puget et al.\textsuperscript{10} performed stereotactic biopsies in 130 pediatric patients with diffuse intrinsic pontine gliomas and 28 patients had grade IV tumors according to histopathologic examination. In the study cohort, only five patients had comorbidities and no mortality related to the biopsy application was reported. Thus, the median OS and PFS were 10.3 and 5.6 months, respectively\textsuperscript{10}.

The characteristic histological appearance consisted of brisk mitotic activity, nuclear polymorphism, hypercellularity, endothelial proliferation, and necrosis. The tumor corresponds to World Health Organization (WHO) grade IV. Low-grade tumors have an insidious onset and course. However, high-grade lesions have an aggressive course with rapid progression commonly resulting to death within the first year of diagnosis\textsuperscript{1,2}. Some specific molecular alterations such as activin-A receptor type 1 (ACVR1) have also been identified in pediatric brainstem gliomas\textsuperscript{11}.

Treatment of brainstem gliomas includes steroids, surgery, RT, and chemotherapy\textsuperscript{11-14}. Chemotherapy has limited effect in brainstem gliomas\textsuperscript{11-29}. Temozolomide and RT combination has been standard approach in treatment of brainstem gliomas\textsuperscript{11-16,18-21,27,28}. However, we reported equivocal results in children treated with temozolomide and RT (Table 2). Nimotuzumab (which targets epidermal growth factor receptor, EGFR) is also used in children with brainstem glioma and reported to have modest benefits on survival time\textsuperscript{11,17,25}. The protocol involving antivasual endothelial growth factor agents: bevacizumab with irinotecan and temozolomide was shown to be feasible and tolerable in pediatric brainstem gliomas (Table 2). However, this protocol was also reported to have limited efficacy in terms of improving survival\textsuperscript{14,18}.

According to literature, there are meta-analyses about the treatment of pediatric high-grade brainstem gliomas\textsuperscript{8,30-32}. Maxwell et al.\textsuperscript{8} used surveillance epidemiology and end results (SEER) database for the study. He enrolled 154 patients with high-grade brainstem gliomas. Median survival for the entire cohort was 10 months. Glioblastoma histology and large tumor size were significantly associated with poor survival rates. Radiation therapy was associated with a decreased risk of mortality at six and nine months but not long-term. On the contrary, extent of surgical resection did not confer any survival advantage at six months, nine months, one year, and two years\textsuperscript{8}. Lam et al.\textsuperscript{32} analyzed 124 pediatric patients with high-grade brainstem gliomas. Patients with grade III gliomas had a median survival of 13 months and those with glioblastoma had a median survival of nine months. In this cohort,
surgical resection was associated with significantly lower mortality, especially in combination with radiation therapy. Radiation therapy alone was significantly associated with decreased mortality within the first nine months after diagnosis but not with overall mortality.\textsuperscript{32}

In most of the patients with brainstem gliomas, we could not perform tumor sampling and histopathological examination, and these patients undergo treatment modalities as high-grade gliomas. There are not any definite rates of high-grade brainstem gliomas in the literature (Table 2). Surgeries including maximal safe resection can be performed only in patients with dorsal exophytic (type III) tumors. However, surgical resection was not associated with significantly lower mortality or good prognosis in these patients.\textsuperscript{8,30-32}

**Conclusion**

This report of three cases suggests that it is important to consider the presence of glioblastoma in the differential diagnosis of brainstem lesions. Definitive diagnosis usually requires histopathological confirmation. Accurate diagnosis of tumor type in the brainstem may lead to changes in therapeutic decisions and potentially the outcome. Treatment of brainstem high-grade gliomas includes steroids, surgery, RT, and chemotherapy. However, none of these treatment modalities really affect survival time. Median OS of these patients is approximately 9 to 12 months in the literature. Glioblastoma histology has been associated with poor prognosis in pediatric patients with high-grade brainstem gliomas. Radiation therapy has been associated with a decreased risk of mortality nine months later but not long term.

**Conflict of Interest**

We declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**References**


