Primitive neuroectodermal tumors of the brainstem in children treated according to the HIT trials: clinical findings of a rare disease

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OBJECT Primitive neuroectodermal tumors of the central nervous system (CNS-PNET) arising in the brainstem are extremely rare, and knowledge about them is limited. The few existing case series report fatal outcomes. The purpose of this study was to analyze clinical characteristics of and outcome for brainstem CNS-PNET patients treated according to the consecutive, population-based HIT studies covering a 19-year time period.

METHODS Between September 1992 and November 2011, 6 eligible children with histologically proven brainstem CNS-PNET not otherwise specified and 2 children with brainstem ependymoblastomas (3, partial resection; 3, subtotal resection; 2, biopsy), median age 3.3 years (range 1.2–10.6 years), were treated according to consecutive multimodal HIT protocols for CNS-PNET/medulloblastoma. Postoperative treatment was according to maintenance chemotherapy protocols (3, craniospinal irradiation [CSI] followed by maintenance chemotherapy), sandwich chemotherapy protocols (2, neoadjuvant chemotherapy, CSI, maintenance chemotherapy), or a therapy protocol for children younger than 4 years (3, postoperative chemotherapy followed by CSI).

RESULTS The median duration of prediagnostic symptoms, predominantly cranial nerve deficits (n = 7), pyramidal tract signs (n = 5), or ataxia (n = 5), was 5 weeks (range 1–13 weeks). The tumors were all located in the pons. Most involved more than half of the pontine axial diameter and were sharply marginated. All patients had postoperative residual disease, including metastasis in 1 case. With 1 exception all tumors progressed early during treatment within 3.9 months (range 2.5–10.4 months), leading to a 1-year event-free survival rate (± standard error) of 13% ± 12%. After progression, patients succumbed early to their disease resulting in a 1-year overall survival rate of 25% ± 15%. The only surviving patient had a partially resected CNS-PNET, received a sandwich chemotherapy protocol, and is without disease progression 14 months after diagnosis.

CONCLUSIONS CNS-PNET is a rare but important differential diagnosis in childhood brainstem tumors. So far, efficient therapies are lacking. The sampling of tumor material for improved biological understanding and identification of new therapeutic targets is important.

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KEY WORDS primitive neuroectodermal tumor; brain tumors; brainstem; children; chemotherapy; radiotherapy; oncology
Brainstem tumors account for 14% of all CNS tumors in the pediatric population. The growth pattern is mostly diffuse pontine (80%). Tumors with focal growth may occur throughout the brainstem, with the medulla oblongata or midbrain being the predominant sites. The largest proportion of brainstem tumors are of glial origin (~90%). While diffuse intrinsic pontine gliomas (DIPGs) are associated with a poor prognosis, the prognosis of focal gliomas is more favorable. Histologically, gliomas need to be distinguished from other less frequent tumor entities, including central nervous system primitive neuroectodermal tumors (CNS-PNETs).

CNS-PNETs typically arise in the supratentorial brain but may also develop in the brainstem or spinal cord. They are a rare tumor entity accounting for only 4.8% of childhood brain tumors. CNS-PNETs are highly malignant embryonal tumors capable of disseminating throughout the CNS. Morphologically, these tumors are very similar to medulloblastomas that arise in the cerebellum or the medulla oblongata. However, there is growing evidence for a different tumorigenesis from molecular genetic studies.21,26 The current WHO classification hence defines CNS-PNET and medulloblastoma as different entities.23 Clinically, CNS-PNETs behave more aggressively and are associated with lower survival rates compared with medulloblastoma.18 In the HIT '91 and HIT 2000 studies for CNS-PNET patients older than 3–4 years, multimodal treatment consisting of surgery, craniospinal irradiation (CSI) plus boosts, and chemotherapy led to 3- to 5-year progression-free survival (PFS) rates of 34% and 47%, respectively.14,32 In children younger than 3–4 years at diagnosis, intensive chemotherapy is often administered in an effort to delay radiotherapy and avoid or reduce the associated neuropsychological sequelae. The HIT-SKK 87/92 and HIT 2000 radiotherapy and avoid or reduce the associated neuropsychological sequelae. The HIT-SKK 87/92 and HIT 2000 protocols displayed in Fig. 1.

Maintenance Chemotherapy Protocols

One patient (Case 1, Table 1) was treated according to the HIT '91 maintenance arm as published previously. He received CSI with 35.2 Gy and a boost to the tumor region to 55.2 Gy, followed by maintenance chemotherapy, as shown in Fig. 1. Two patients were treated with reduced conventional fractionated CSI of 23–24 Gy and a boost to the tumor region to 54–55 Gy, as recommended in the HIT 2000 maintenance protocol for nonmetastatic medulloblastoma patients aged > 4 years at diagnosis. After radiotherapy, one of these 2 patients (Case 2) received 2 courses of maintenance chemotherapy.

Sandwich Chemotherapy Protocols

Two patients were treated according to the HIT 2000 sandwich chemotherapy protocol with 2 cycles of SKK chemotherapy (Fig. 1). One patient (Case 5) subsequently received hyperfractionated CSI with 36.0 Gy (2 x 1.0 Gy daily) and a boost to the tumor region up to 67.0 Gy, and the other patient (Case 4) was treated with 36.0 Gy conventional fractionated CSI and a boost to the tumor region up to 60.0 Gy. The CSI was followed by up to 4 courses of maintenance chemotherapy (Fig. 1).

HIT 2000 Standard SKK Chemotherapy Protocol for Young Children

Three patients started treatment with SKK chemotherapy according to the HIT 2000 protocol for young children with nonmetastatic CNS-PNET (Fig. 1, Table 2). In 1 child with metastatic disease (Case 6, Table 1), an intraventricular access device (Omaya reservoir) was implanted after histological diagnosis of ependymoblastoma, and intraventricular methotrexate was given concomitantly to the SKK chemotherapy according to the guidelines described for nonmetastatic medulloblastoma in young children.
Diagnostic Evaluations and Follow-Up

Staging recommendations consisted of a craniospinal MRI and evaluation of CSF. Central review was offered for imaging and CSF analysis. If tumor cells were present in the CSF, an analysis should be obtained ≥ 14 days after surgery and before postoperative treatment. The extent of surgery based on the surgical report and postoperative MRI was defined as gross-total resection if no residual tumor was detectable, subtotal resection if > 90% of the tumor volume was removed, partial resection if > 10%–90%, and biopsy if ≤ 10% was removed. Postoperative imaging was performed 24–48 (–72) hours after surgery. The extent of postoperative residual tumor was calculated as an area in order to allow better comparison to other studies. Partial response, improvement, stable disease, and progressive disease were defined, respectively, as a ≥ 50% decrease, 25%–50% decrease, < 25% decrease or increase, and ≥ 25% increase (or new metastasis) in the tumor volume on MRI. Imaging was to be repeated every 3–4 months in the first 2 years after treatment, every 6–9 months up to 5 years after treatment, and annually thereafter.

Brainstem tumors were retrospectively analyzed for their focality and other neuroradiological characteristics.

The table below shows detailed patients’ tumor and treatment characteristics:

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pt Age (yrs), Sex</th>
<th>Histology</th>
<th>EOR</th>
<th>Residual Tumor*</th>
<th>Stage</th>
<th>Treatment Protocol</th>
<th>Craniospinal RT</th>
<th>Time to Progression (mos)</th>
<th>Failure Type</th>
<th>Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.6, M</td>
<td>CNS-PNET</td>
<td>Biopsy</td>
<td>&gt;1.5 cm²</td>
<td>M0/1</td>
<td>HIT ’91 maintenance</td>
<td>SRT</td>
<td>8.2</td>
<td>Local</td>
<td>DOD (11.3)</td>
</tr>
<tr>
<td>2</td>
<td>2.2, F</td>
<td>CNS-PNET</td>
<td>Partial</td>
<td>Yes</td>
<td>M0</td>
<td>HIT 2000 maintenance</td>
<td>SRT</td>
<td>6.0</td>
<td>Local</td>
<td>DOD (8.0)</td>
</tr>
<tr>
<td>3</td>
<td>5.5, F</td>
<td>CNS-PNET</td>
<td>Subtotal</td>
<td>&gt;1.5 cm²</td>
<td>M0</td>
<td>HIT 2000 maintenance</td>
<td>SRT</td>
<td>4.0</td>
<td>Local</td>
<td>DOD (5.6)</td>
</tr>
<tr>
<td>4</td>
<td>4.4, M</td>
<td>CNS-PNET</td>
<td>Partial</td>
<td>&gt;1.5 cm²</td>
<td>M0</td>
<td>HIT 2000 sandwich</td>
<td>SRT</td>
<td>NA</td>
<td>NA</td>
<td>AWD (13.6)</td>
</tr>
<tr>
<td>5</td>
<td>6.0, F</td>
<td>CNS-PNET</td>
<td>Subtotal</td>
<td>Yes</td>
<td>M0</td>
<td>HIT 2000 sandwich</td>
<td>HFRT</td>
<td>10.4</td>
<td>Local</td>
<td>DOD (22.7)</td>
</tr>
<tr>
<td>6</td>
<td>1.2, M</td>
<td>EBL</td>
<td>Subtotal</td>
<td>&gt;1.5 cm²</td>
<td>M1+3</td>
<td>Standard SKK</td>
<td>NA</td>
<td>2.6</td>
<td>Local</td>
<td>DOD (6.7)</td>
</tr>
<tr>
<td>7</td>
<td>1.8, F</td>
<td>CNS-PNET</td>
<td>Biopsy</td>
<td>&gt;1.5 cm²</td>
<td>n.d.</td>
<td>Standard SKK</td>
<td>NA</td>
<td>2.8</td>
<td>Local</td>
<td>DOD (3.2)</td>
</tr>
<tr>
<td>8</td>
<td>1.9, M</td>
<td>EBL</td>
<td>Partial</td>
<td>&gt;1.5 cm²</td>
<td>M0</td>
<td>Standard SKK</td>
<td>NA</td>
<td>2.5</td>
<td>Local</td>
<td>DOD (4.1)</td>
</tr>
</tbody>
</table>

AWD = alive with disease; DOD = dead of disease; EBL = ependymoblastoma; EOR = extent of resection; HFRT = hyperfractionated radiotherapy; M0 = nonmetastatic disease; M1 = tumor cells in CSF; M0/1 = no macroscopic metastasis; M2 = cranial metastasis; M3 = spinal metastasis; NA = not applicable; n.d. = not done; Pt = patient; RT = radiotherapy; SRT = standard radiotherapy.

* On early postoperative MRI.
by an experienced neuroradiologist (M.W.-M.) using the initial MRI studies. Focal brainstem tumors were considered to be limited to one anatomical brainstem segment and occupying not more than 50% of this segment as defined by Barkovich et al. A delineated tumor margin was not defined to be a criterion for focality, because a lot of DIPGs have it in clinical praxis as well.

Statistical Analysis

Data were documented and analyzed at the HIT ’91/HIT 2000 trial center at the Children’s University Hospital of Hamburg-Eppendorf, Germany (until 2009: Children’s University Hospital of Wuerzburg, Wuerzburg, Germany). Radiotherapy data were collected at the Department of Radiation Oncology, University of Leipzig, Germany. Survival was estimated by the Kaplan-Meier method. Overall survival (OS) was defined as date of diagnosis to death of any cause, the date of last visit specified censoring. Event-free survival (EFS) was defined as the time from the date of diagnosis to the date of first progression, relapse, occurrence of secondary malignancy, death of any cause, or last contact–specified censoring. Analysis was performed with the SPSS software, version 18.0.

Results

Patient Characteristics

Tumor and treatment characteristics of the 8 patients (4 female) with brainstem CNS-PNET are displayed in Table 1. The median age at diagnosis (date of surgery) was 3.3 years (range 1.2–10.6 years). The median duration of time from the manifestation of the first symptoms to diagnosis was 5 weeks (range 1–13 weeks). On baseline medical examination, pyramidal tract signs (n = 5) and ataxia (n = 5) were the most common neurological signs (Fig. 2). Symptoms of cranial nerve (CN) lesions affected CN VII (n = 4), CN VI (n = 3), CN III (n = 1), and CN IX (n = 1) (Fig. 2). All patients had either ataxia or a pyramidal tract deficit or a cranial nerve deficit. Three of 8 patients had the triad of symptoms simultaneously. No patient had symptomatic hydrocephalus or required a ventriculoperitoneal shunt at diagnosis. In 6 patients an open tumor resection was performed. In 3 of these patients the tumor was accessed through the fourth ventricle, via a midline occipital craniotomy and incision of the cerebellar vermis, and in the other 3 patients through the cerebellopontine angle, via a lateral craniotomy. The neurosurgeons documented the use of neuronavigation in 3 of 6 cases and neuromonitoring in 4 of 6 cases in their surgery reports. Surgery led to partial resection in 3 cases and subtotal resection in 3 cases. In 2 patients surgery was rated as not feasible by neurosurgeons, and stereotactic biopsies were performed. On postoperative MRI all patients had residual tumor. The extent was > 1.5 cm² in 6 and not reasonably determinable in 2 patients (Table 1). In the immediate postoperative period, neurological deficits remained almost unchanged from those observed at initial presentation (Fig. 2). Central review of histology was obtained in 6 of 8 cases. The tumors were classified as CNS-PNET not otherwise specified in 6 cases and ependymoblastoma in 2 cases. At diagnosis 7 patients had no evidence of metastasis (5, complete...
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staging, M0; 1, craniospinal MRI but no CSF analysis, M0/1; 1, no spinal MRI or CSF staging), and 1 patient had macroscopic spinal metastases (M3) with tumor cells in the CSF (M1).

Neuroradiological Characteristics

Initial cranial MRI studies from 6 of 8 patients with brainstem CNS-PNETs were available for review (Table 2, Fig. 3). The principal part of all tumors was in the pons—plus additionally in the peduncle in 1 patient. In 4 of 6 patients, the tumors had an eccentric location within the pons. Four of the tumors were diffuse, because they involved more than half of the pontine axial diameter. They had sharp tumor margins against the adjacent tissue. The remaining 2 tumors were focal because they had a size of less than one-half of the pons. Their margins were blurred. Fiber tracts were not preserved within the tumors. Only 1 tumor displayed exophytic expansion to the fourth ventricle. Encasement of the basilar artery was seen in 2 patients. Two other patients had a tumor cyst or tumor necrosis with bleeding residues. No peritumoral edema was seen in any of the initial MRI studies. All 6 tumors showed a predominantly low signal on T1-weighted images and a bright signal on T2-weighted images, but the signals were often inhomogeneous. Gadolinium was administered to all patients intravenously, showing a contrast uptake within the tumor in 4 of 6 patients (focal in 3, multifocal in 1).

Clinical Course After Surgery

All patients treated with the maintenance chemotherapy protocols (n = 3) relapsed shortly after CSI (n = 1) or during subsequent maintenance chemotherapy (n = 2) (Fig. 4). Five patients were treated with up-front chemotherapy before the planned radiotherapy (Fig. 4). All 3 young children had disease progression after not more than 1 cycle of SKK chemotherapy. The 2 patients treated according to the HIT 2000 sandwich chemotherapy protocol (Fig. 1) received 2 cycles of SKK chemotherapy, followed by CSI and maintenance chemotherapy (Fig. 4). One of these patients had disease progression during maintenance chemotherapy, whereas the other patient is the only progression-free survivor of the whole study group, having a residual tumor at last follow-up 14 months since diagnosis as of this writing.

The EFS for the 8 brainstem CNS-PNET patients was 2.5, 2.6, 2.8, 4.0, 6.0, 8.2, 10.4, and 13.6 months, leading to a 1-year EFS rate (± standard error) of 13% ± 12%. Excluding the progression-free patient, the median time to progression was 3.9 months (range 2.5–10.4 months). The OS for all patients was 3.2, 4.1, 5.6, 6.7, 8.0, 11.3, 13.6, and 22.7 months, leading to a 1-year OS rate of 25% ± 15%. The Kaplan-Meier curves of EFS and OS are shown in Fig. 5.

All treatment failures were local relapses. Two patients received further therapy in curative intention (1, chemotherapy including high-dose chemotherapy; 1, chemotherapy) and 2 patients received palliative treatment (1, surgery; 1, surgery, chemotherapy, hyperthermia). In all cases of disease progression, the patients succumbed to their disease (median survival time 2.0 months, range 0.5–12.2 months).

Discussion

This multiinstitutional prospective observational study is to our knowledge the largest report of CNS-PNET primarily localized in the brainstem. Eight children were registered in the consecutive, population-based HIT studies over a 19-year period, demonstrating the rareness of disease. The reported incidence of CNS-PNET among brainstem tumors is variable. In two series, 5 (17%) of 30 and 7 (5%) of 146 children with brainstem tumors had the histological diagnosis of a CNS-PNET.3–5,36 The vast majority of these tumors were described as focal mass lesions. In 2 of the 6 cases in which initial MRI studies were available in our cohort, the tumors were defined as focal. The other 4 tumors were diffuse, but unlike DIPG, the tumors did not show a typical diffuse infiltrative appearance, did not split fiber tracts, and had an eccentric location within the pons. Only patients with brainstem tumors that were resected or biopsied, offering the possibility for pathological diagnosis, were registered into this study. The diagnosis of DIPG with a typical growth pattern is currently based on

FIG. 2. Neurological deficits of all brainstem CNS-PNET patients (n = 8) before (white) and immediately after (gray) surgery. Numbers in the boxes represent the individual cases of Table 1.
MRI, and biopsy at the time of diagnosis or autopsy is not mandatory. Diffuse infiltrative CNS-PNETs have been described in postmortem examinations of brainstem tumors that were initially diagnosed as typical DIPGs based on MRI examinations.\(^1,31\) Thus, it is possible that CNS-PNETs with such growth patterns are underdiagnosed and for this reason were not represented in our patient cohort.

The median age of our patients at diagnosis of brainstem CNS-PNET was lower (3.3 years) than in patients with brainstem glioma (range 7–9 years).\(^8,22\) Combining our data with those of the largest series published so far, the median age at diagnosis of 25 children with brainstem CNS-PNET was 3.1 years (range 0.2–14.8 years).\(^5,10,36\) It has been suggested before that brainstem CNS-PNETs develop at a younger age than brainstem gliomas.\(^36\) However, 5 of 25 patients were older than 7 years and in the age range that is considered typical for brainstem glioma.

Clinical symptoms observed in our study resembled the symptoms caused by DIPG or brainstem high-grade glioma\(^3,11\) rather than those of focal low-grade glioma:\(^3,11,1\) 1) The mean duration of symptoms until diagnosis was short (5 weeks). 2) All patients had typical symptoms, consisting of cranial nerve dysfunction, pyramidal tract signs, and ataxia related to the pontine location of the tumor. A great portion of the patients even had all of the symptoms simultaneously.

One of the 8 patients in our cohort had metastatic disease at diagnosis. In the series reported by Zagzag et al., 3 of 7 patients presented with metastatic disease at diagnosis.\(^36\) In supratentorial CNS-PNET, the incidence of metastatic disease ranges from 13% to 27%.\(^18\) For that reason, a complete initial staging—including craniospinal MRI and lumbar CSF analysis—is strongly recommended, and the radiotherapy should encompass the whole CSF space. In contrast to CNS-PNET, metastatic disease at diagnosis is very uncommon in brainstem glioma, although published trials have not always required a complete craniospinal staging before inclusion of patients.\(^7\)

All but one of our patients with brainstem CNS-PNET developed early disease progression and succumbed to...
their disease. In two other studies the outcome was equally fatal.5,36 Although conclusions are limited by small patient numbers, it seems to be more difficult to achieve tumor control in brainstem CNS-PNET patients compared with medulloblastoma or supratentorial CNS-PNET patients. Our results do not suggest that one of the postoperative treatment modalities used first (chemotherapy or radiotherapy) would result in better tumor control than the other. After treatment according to the Head Start I and II protocols using intensive chemotherapy (including high-dose chemotherapy) and CSI, 2 of 6 brainstem CNS-PNET patients were alive without active disease.10 Although these results are promising, it needs to be proven with higher patient numbers, whether such an intensive treatment concept is superior to conventional chemotherapy regimens plus radiotherapy, as used in our patients.

Most likely, the anatomical location contributes to the unfavorable prognosis of brainstem CNS-PNET. In prospective studies postoperative residual tumor was not a prognostic factor in supratentorial CNS-PNET patients. However, this could be related to the small patient numbers, because there was often a trend toward a worse outcome.18 In our cohort 6 of 8 patients received subtotal/partial resection without an increase in postoperative neurological deficits. However, the postoperative residual tumor was still > 1.5 cm² in most cases. A complete resection of CNS-PNET is difficult to achieve in the brainstem without risking severe permanent neurological deficits. Therefore, the extent of resection remains to be determined on an individual basis.

The tumor location of brainstem CNS-PNET adjacent to the cerebellum raises the question whether its tumorigenesis could be linked to that of medulloblastoma. Re-
cently, it has been shown in mouse models that certain histological subtypes of medulloblastoma can develop from cells with brainstem origin.\textsuperscript{13,17} Recently, it has been suggested that supratentorial CNS-PNETs constitute a heterogeneous group of tumors that can largely be reclassified to other brain tumor types through the use of molecular-genetic methods.\textsuperscript{20} However, gene expression analysis of 2 diffuse pontine CNS-PNETs displayed a closer relation to supratentorial CNS-PNET than to medulloblastoma.\textsuperscript{21} Thus, tissue banking and pooling of samples from large study groups is important in order to gain more insights in the biological properties allowing better classification of these tumors and to identify targets for new treatments.

Conclusions

Brainstem CNS-PNETs are associated with young age, a short clinical history at initial presentation, and severe neurological symptoms. Focal brainstem masses in patients with these clinical findings should be biopsied, whenever appropriate. Relapses occur mostly locally and very early during postoperative multimodal treatment, leading to a dismal prognosis. It remains to be clarified, if patients can benefit from improved, intensive (high-dose) chemotherapy and craniospinal radiotherapy or new treatment strategies. Histological verification of diffuse pontine brainstem tumors in the setting of clinical trials or postmortem examination will allow for learning more about the incidence of CNS-PNET among DIPGs diagnosed by MRI. Molecular-genetic analysis of tumor material may help to delineate the biological origin(s) of this tumor entity in this special location as a first step toward a more targeted therapy in the future.

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References

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