Primary cerebral neuroblastoma

Long-term follow-up review and therapeutic guidelines

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Primary cerebral neuroblastoma is a distinct pathological and clinical entity that differs from other primitive neuroectodermal tumors. To characterize the clinical course of this lesion, the authors performed a retrospective analysis in 11 patients who ranged in age from 17 months to 26 years. The tumor had no predilection for either sex. Signs and symptoms were mostly those associated with increased intracranial pressure. The lesions commonly involved the parietal and occipital lobes. Computerized tomography scans of nine patients showed five solid and four cystic lesions; calcifications were found more commonly in the solid lesions. Contrast enhancement was seen in all tumors, yet angiograms typically showed an avascular mass. Total removal of tumor was possible in only two patients, both with cystic tumors. The remaining nine underwent subtotal resection of a solid lesion (in five) or a cystic lesion (in four). All 11 patients underwent postoperative irradiation that included the spinal axis in two cases; only one received adjuvant chemotherapy (solid tumor). Four patients, all with solid tumors that initially were subtotally resected, had evidence of tumor recurrence. The only patient with a subtotally resected solid lesion who did not have recurrence received adjuvant chemotherapy. The six patients who had cystic lesions are free of recurrent tumor at 26 to 109 months after surgery. Based on follow-up analysis of the 11 patients, recommendations are proposed for the treatment of primary cerebral neuroblastomas.

KEY WORDS: cerebral neuroblastoma · neuroblastoma · primitive neuroectodermal tumor · solid tumor · cystic tumor

SUPRATENTORIAL gliomas are uncommon tumors in children, constituting 10% to 14% of all intracranial tumors in the pediatric age group. The majority of these neuroectodermally derived neoplasms are of astrocytic and ependymal origin. They most commonly involve the cerebral hemispheres, opposed to the midline structures. Primitive neuroepithelial tumors are the least common of these supratentorial tumors, and they pose the greatest diagnostic difficulty, preoperatively as well as pathologically.

In 1976, Horten and Rubinstein analyzed 35 cases of primary cerebral neuroblastoma and characterized this tumor as a distinct clinicopathological entity that differs from other similar primitive neuroectodermal neoplasms. The prognosis and appropriate treatment for these tumors is still controversial. We retrospectively analyzed 11 patients with the diagnosis of primary cerebral neuroblastoma to determine if length of survival is dependent on tumor morphology, the extent of surgical resection, and the use of radiation therapy.

Clinical Material and Methods

Clinical Data

Eleven patients, five females and six males, with the diagnosis of primary cerebral neuroblastoma were treated on the Neurosurgical Service of the University of California, San Francisco, between 1972 and 1979 (Table 1). The age at which these patients first exhibited symptoms ranged from 17 months to 26 years (mean 9.9 years). The duration of clinical symptoms before diagnosis ranged from 3 days to 2 years. The most common presenting symptoms were referable to increased intracranial pressure; there were relatively few clinical signs on presentation, mild hemiparesis being the most prevalent (in four), followed by papilledema and decreased visual acuity. Two of the tumors were
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Location of Tumor</th>
<th>Symptoms*</th>
<th>Presenting Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 yrs, F</td>
<td>rt parietal</td>
<td>cranial bruit</td>
<td>normal examination</td>
</tr>
<tr>
<td>2</td>
<td>6 yrs, M</td>
<td>rt parietal</td>
<td>weakness, LUE</td>
<td>mild paresis, LUE</td>
</tr>
<tr>
<td>3</td>
<td>9 yrs, F</td>
<td>rt occipital</td>
<td>HA, N/V, blurred vision</td>
<td>decreased visual acuity; papilledema</td>
</tr>
<tr>
<td>4</td>
<td>7 yrs, F</td>
<td>lt basal ganglia</td>
<td>HA, N/V</td>
<td>decreased visual acuity; papilledema</td>
</tr>
<tr>
<td>5</td>
<td>12 yrs, M</td>
<td>rt frontal</td>
<td>lt focal seizures with generalization; decreased memory</td>
<td>normal examination</td>
</tr>
<tr>
<td>6</td>
<td>11 yrs, M</td>
<td>rt occipital</td>
<td>HA</td>
<td>normal examination</td>
</tr>
<tr>
<td>7</td>
<td>11 yrs, F</td>
<td>lt occipital</td>
<td>HA, N/V</td>
<td>decreased visual acuity papilledema; mild lt hemiparesis</td>
</tr>
<tr>
<td>8</td>
<td>26 yrs, M</td>
<td>rt parietal</td>
<td>HA, blurred vision; occasional confusion</td>
<td>normal examination</td>
</tr>
<tr>
<td>9</td>
<td>13 yrs, M</td>
<td>lt temporoparietal</td>
<td>decreasing memory</td>
<td>normal examination</td>
</tr>
<tr>
<td>10</td>
<td>17 mos, F</td>
<td>rt frontal</td>
<td>left-sided weakness, N/V, irritable</td>
<td>lt hemiparesis</td>
</tr>
<tr>
<td>11</td>
<td>10 yrs, F</td>
<td>lt parietal</td>
<td>lt focal seizures with generalization; rt arm paresthesias</td>
<td>mild rt hemiparesis; increased rt reflexes; mild rt sensory deficit</td>
</tr>
</tbody>
</table>

*LUE = left upper extremity; HA = headache; N/V = nausea and vomiting.

located in the frontal lobe, four in the parietal lobe, three in the occipital lobe, one in the temporoparietal region, and one in the basal ganglia. Seven tumors were in the right and four were in the left hemisphere.

**Diagnostic Studies**

Eight patients underwent angiography; seven showed an avascular mass lesion, and in one patient a faint vascular tumor blush was identified. Nine patients underwent computerized tomography (CT) scanning; a predominantly solid mass was observed in five patients (Fig. 1), and four had a large cystic lesion with a peripheral solid component (Fig. 2). Regardless of the characteristics they demonstrated on the CT scans, all tumors showed heterogeneous contrast enhancement. Calcification was seen in four (80%) of the five solid lesions and in two (50%) of the four cystic lesions. Two patients, who did not undergo CT scanning, were found to have cystic tumors at surgery.

**Treatment**

All 11 patients underwent craniotomy. Gross total removal of the tumor was possible in only two cases; in both, the tumor was cystic with a solid mural nodule. The other nine patients underwent known subtotal resection of the tumor; in five the tumor was solid, and in four it was cystic with a peripheral solid component that varied in size and consistency. There was no operative mortality or postoperative morbidity.

All 11 patients received radiation therapy postoperatively. The mean dose to the tumor was 5236 rads (range 4500 to 6360 rads). Fractionated doses (range 28 to 33, mean 30) were administered over a period of 37 to 49 days (mean 43 days). Nine patients received local irradiation with wide margins to the tumor bed. Two patients with solid lesions underwent craniospinal irradiation. One patient with a solid tumor received seven courses of adjuvant chemotherapy with a combination of procarbazine, CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), and vincristine (PCV).

**Histological Data**

The diagnosis of primary cerebral neuroblastoma was made by light microscopy in all cases. One tumor was examined by electron microscopy also. The cellular morphology of all tumors was similar, consisting of sheets of closely compacted small cells with round-to-oval hyperchromatic nuclei (Fig. 3). Nuclear vesiculation was evident in various degrees, and frequently the nucleoli were not prominent. There was scant cytoplasm. In specimens that included adjacent brain tissue, a well demarcated border zone existed between the tumor and the normal brain tissue. The degree of vascularity varied from moderate to marked, and oc-

**FIG. 1.** Left: Contrast-enhanced computerized tomography (CT) image of a solid cerebral neuroblastoma. Calcified portions of the tumor were demonstrated on the precontrast CT scan. Right: Nonecalcified enhancing mass lesion in the parietal region.
casional areas of necrosis were noted. Mitoses, although present in most specimens, were usually few. Homer Wright rosettes were found in most cases. Silver staining showed no significant areas of neuronal differentiation, although axonal processes were identified in a few specimens. Phosphotungstic acid-hematoxylin (PTAH) staining for glial elements was negative, and immunoperoxidase staining, performed in one case, did not reveal glial fibrillary acidic protein. Electron microscopy of tissue from one tumor showed no secretory granules, neurotubules, or abnormal synaptic junctions.

### Operative Results

Four of the 11 patients had tumor progression that was confirmed by sequential CT scans. All four patients had solid tumors that had been subtotally resected. The time between the prior operation and the diagnosis of tumor progression ranged from 8 months to 31 months (mean 19.2 months). None of the six patients with a cystic tumor had recurrence; four of these tumors had been subtotally resected and two had been totally removed. The seventh patient in whom the tumor did not recur had a solid tumor that was subtotally resected, and was the only patient who received a full course of adjuvant chemotherapy.

The treatments used at the time of tumor progression were as follows: two patients had a second operation as the only form of treatment. In one (Case 8), the recurrent tumor was totally resected, and the other (Case 2) had a subtotal resection. The remaining two patients had a second course of irradiation directed to the tumor and received chemotherapy: Case 4 received irradiation (3000 rads) plus two courses of combined therapy with PCV, nitrogen mustard + vincristine + prednisone + procarbazine (MOPP), and hydroxyurea (HU); and Case 10 had irradiation (4000 rads) plus two courses of chemotherapy with dacarbazine (DTIC), cytoxan, and PCV.

The survival data for all patients are summarized in Tables 2 and 3. Four patients had recurrent solid lesions. One of these, who was 17 months old at the time of the initial diagnosis, had recurrence 13 months later; the patient survived 10 months from the time of recurrence, for a total survival period of 23 months. The second patient, who was 6 years old at the time of the initial diagnosis, had recurrence 25 months later; this patient survived 4 months from recurrence, for a total survival period of 29 months. Neither of these patients survived their age at diagnosis plus 9 months (Collins' Law). The other two patients with recurrent solid tumors are alive at 52 months and 64 months, respectively, from the time of their original diagnosis. In one of them, the time to recurrence was 31 months, at which time the patient received chemotherapy and a second course of radiation therapy. The other patient had a second operation that achieved total removal of the tumor 8 months after the initial surgery.

Seven patients are alive and stable with no evidence of tumor progression, either clinically or on CT scan (Table 3). In contrast to the group of patients with tumor recurrence, only one of the survivors who did
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Table 3
Survival time in seven patients without tumor recurrence

<table>
<thead>
<tr>
<th>Type of Resection</th>
<th>Survival Time (mos)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Solid Tumor</td>
</tr>
<tr>
<td>gross total</td>
<td>52*</td>
</tr>
<tr>
<td>subtotal</td>
<td>52*</td>
</tr>
<tr>
<td></td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>78</td>
</tr>
</tbody>
</table>

* Only one patient received adjuvant chemotherapy (vincristine; seven courses).

not have recurrence had a solid tumor that was subtotally resected. This patient is stable 52 months postoperatively. The remaining six patients had predominantly cystic tumors. Two patients whose tumors were removed totally are alive at 57 and 78 months after operation, respectively. The other four patients, who initially had a subtotal resection, are clinically stable at 26 months to 109 months after their operation.

Discussion and Therapeutic Guidelines

The cellular constituents of the primitive neural tube are a homogeneous cell type of known multipotentiality, and are collectively called the neuroepithelial matrix. These cells are in Stage I or neurocytogenesis, which is an active phase of neural development when mitoses are frequent but cellular differentiation has not occurred. The second stage of cytogenesis marks the origin of the neuroblast, which results from the division of a primitive neuroepithelial matrix cell. These differentiated matrix cells lose their ability to divide further, but they retain the potential for further maturation. It is not until Stage III of cytogenesis that immature glial precursors can be identified; it is these precursors that eventually form astrocytes, oligodendrocytes, and ependymal cells (Fig. 4).

If primary cerebral neuroblastomas do in fact develop de novo, then their cells of origin emerge during the second stage of cytogenesis. The resulting tumor, therefore, is of a neuroblastic type, and its cells have the potential for varying degrees of maturation along one cell line toward neurons. The finding of elements other than primitive neuronal cells (such as spongioblasts or ependymoblasts) would therefore preclude the tumor from being a neuroblastoma, and instead would indicate a mixed neuroectodermal tumor. Such a tumor has been described by other authors as a primitive neuroectodermal tumor (PNET), an entity that must be distinguished from neuroblastoma.

Cushing was one of the early proponents of the term "cerebral neuroblastoma." After reevaluating 11 supratentorial tumors that he had originally described as medulloblastoma, he decided that five of the lesions, although they resembled medulloblastoma, had clinical features different from those of medulloblastoma; all but two of these five tumors had been removed from the cerebrum of an adult. The tumors were slow growing well circumscribed lesions that had only rarely metastasized to the leptomeningeal spaces. They had a propensity to become large and calcify, and were composed principally of neuroblasts. Rubinstein also believed that the tumors many authors labeled "medulloblastoma," "ependymoma," "poorly differentiated oligodendroglioma," or "undifferentiated primary sarcoma" were probably neuroblastomas. He proposed that the following three features could differentiate neuroblastoma from other recognized primitive neuroectodermal tumors: 1) they are generally well circumscribed lesions with limited areas of microscopic invasion of neoplastic cells into adjacent brain; 2) they often have prominent reactive gliosis at the tumor margin; and 3) they have a matrix of connective tissue of varying density which is not always adjacent to areas of leptomeningeal invasion by the tumor.

Horton and Rubinstein classified neuroblastomas on the basis of the degree of connective tissue present, differentiating "classic" lesions with scant connective tissue from the "desmoplastic" variant, which they identified as having a more prominent stroma, especially when the tumor was located adjacent to the leptomeninges. They also distinguished a transitional type of neuroblastoma. Ganglion cells were more often found in the "classic" tumor, suggesting that mature neuronal cells may induce less of a stromal reaction than is seen with the more primitive precursor cells. Other investigators have demonstrated a similar degree of connective tissue component, although they have not used Horton and Rubinstein's classification system.

Although some authors support the theory that neuroblastomas are a distinct pathological and clinical entity, others feel that neuroblastoma is an "unfortunate" or "restrictive" term, and doubt its validity. We believe that there is sufficient evidence to warrant the conclusion that other primitive neuroectodermal tumors belong in a classification distinct from neuroblastomas, the primary feature of these other tumors being glial elements and precursors, and varying degrees of neuronal cell differentiation.
The gross histological characteristics of neuroblastomas are not helpful in differentiating them from other primitive neuroectodermal tumors. As seen by light microscopy, the histological pattern of a neuroblastoma is that seen in the cases described earlier. Other primitive neuroectodermal neoplasms, such as medulloepithelioma, polar spongioblastoma, ependymoblastoma, and cerebellar medulloblastoma, can often be distinguished from the neuroblastoma on the basis of the following histological features: glial differentiation (PTAH-positive fibrils), 90% to 95% cellular nondifferentiation, a greater degree of cellular pleomorphism and endothelial hyperplasia, and a less prominent connective tissue component. Nonetheless, differentiation between the neuroblastoma and the other primitive neuroectodermal tumors may be difficult on light microscopy because of the variability of their histological features. However, electron microscopic analysis of the cellular ultrastructure has been used to confirm the diagnosis of neuroblastoma in selected cases.

Horton and Rubinstein noted that, in 85% of their patients, the symptoms of cerebral neuroblastoma began during the first 10 years of life; and in 77% of these, symptoms appeared during the first 5 years of life. There was no apparent predominance in either sex. The tumors occurred slightly more commonly in the left hemisphere. They were found to arise in any lobe, but, as others had confirmed, they had a predilection for the frontal and parietal regions. In addition, the symptoms and signs accompanying the lesion were those related to increased intracranial pressure.

Roentgenographic features are not useful in distinguishing primary cerebral neuroblastomas from other primitive neuroectodermal neoplasms. Angiograms typically reveal an avascular mass lesion, but occasionally a vascular blush may be present. The CT scans characteristically demonstrate either large cystic tumors with an accompanying mural nodule or a predominantly solid mass. Both types of lesions frequently show calcification and prominent contrast enhancement. Similar angiographic and CT findings were observed in our 11 patients.

Patients with peripheral neuroblastomas characteristically have elevated levels of catecholamine metabolites in the urine and blood. Similar findings have not been demonstrated in patients harboring primary cerebral neuroblastomas, however; such patients in whom plasma and urine catechols have been measured have had normal levels. Determinations of catecholamine levels in cerebrospinal fluid (CSF), plasma, and urine were not obtained in any of our patients, nor was an analysis of tumor tissue performed.

Nine of Horten and Rubinstein's patients who survived their first operation had tumor recurrence between 6 months and 7 years postoperatively. Detailed case histories of five of these patients revealed that three harbored solid tumors and two had cystic lesions. Postoperative radiation therapy was given to three of these patients (two with a solid tumor, and one with a cystic tumor). Adjuvant chemotherapy was administered to only one patient with a cystic lesion.

The recurrence of solid tumors in patients who have undergone subtotal resection or total removal and radiation therapy has been noted by others; none of these reported patients received a full course of adjuvant chemotherapy. In our series, patients with solid tumors who underwent a subtotal resection had the worst prognosis; the only such patient in our series to survive received a full course of adjuvant chemotherapy.

None of our patients with a cystic tumor had recurrence. In our review of the literature, we have found only four cases of tumor recurrence in patients with cystic tumors initially; three patients had undergone total removal of the tumor, and one had a subtotal resection. Only one of these patients had received radiation therapy postoperatively.

We have had experience previously with 40 patients harboring glial tumors who were treated at the time of recurrence with local or craniospinal irradiation to doses as high as 4000 rads. Although all of these patients eventually died as a result of their original tumor, none developed radiation necrosis. Based on these data, we instituted repeat irradiation for two of our patients who had tumor recurrence. Both showed signs of improvement clinically and on CT scan, and suffered no deleterious effects.

Autopsy findings in Horten and Rubinstein's entire series revealed evidence of leptomeningeal or ventricular dissemination of tumor, or both, in 38% of the patients. Yet some of their patients with verified metastases lived longer than those who did not have craniospinal and/or extraneural dissemination. In view of this finding, and considering reports such as that of Percy, et al., in which 60% of patients with primary tumors of the central nervous system discovered initially at the postmortem examination had been asymptomatic during life, it would seem that CSF invasion and/or extraneural metastases may not always be a critical factor in the patient's clinical outcome.

In summary, primary cerebral neuroblastomas merit separate consideration from other primitive neuroectodermal tumors. Clinically, radiologically, and morphologically at operation, they are indistinguishable, yet histologically and biologically they are distinct. Primary cerebral neuroblastomas should be radically excised when possible, followed by irradiation, with wide margins, to the tumor bed. Although spinal axis irradiation has been recommended by some, we believe it should be reserved for cases in which the myelogram or CSF cytology determination shows evidence of tumor dissemination. Adjuvant chemotherapy should be considered in patients whose solid tumors were subtotally resected. When feasible, recurrence should be treated by reoperation followed by local irradiation.
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In addition, chemotherapy should be considered. In comparison with patients who have other primitive neuroectodermal tumors, those with primary cerebral neuroblastomas have a much better prognosis for long-term survival.

References


Manuscript received September 27, 1982. Accepted in final form March 10, 1983.
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