Brain Tumors in Children: A Review*

ALVARO LACAYO, M.D.,†
and PETER M. FARMER, M.D.‡

Departments of Neurology† and Pathology‡,
North Shore University Hospital
and Department of Pathology†,
Cornell University Medical College
Manhasset, NY 11030

ABSTRACT

Brain tumors are the second most common malignancy of children. In contrast to adults, childhood brain tumors are usually of glial origin; metastases and meningiomas are rare. Some tumors, i.e., medulloblastomas, are found almost exclusively in children. The posterior fossa is the most frequent site of occurrence. The prognosis for childhood neoplasms tends to be more favorable than in adults, and some lesions are curable. New techniques, including immunostaining, tumor markers, and cytogentic, have improved diagnostic accuracy. A review of some of the most important brain tumors of children is presented along with an upgrade on recent developments in diagnoses and treatment.

Introduction

Intracranial tumors are the second most common group of neoplasms in children, exceeded only by the leukemias. The estimated incidence of brain tumors in patients under 15 years of age ranges from 2.5 to 3.5 per 100,000. There is distinct familial trend in pediatric brain tumors. The inherited neurocutaneous disorders are regularly associated with intracranial neoplasms. Gliomas are frequently seen with neurofibromatosis; subependymal giant cell astrocytomas with tuberous sclerosis; capillary hemangioblastomas with von Hippel-Lindau disease; and basal-cell nevus syndrome with medulloblastoma. A higher incidence of brain tumors has been observed in patients with a strong family history of seizures and stroke.

The posterior fossa is the most frequent location of brain tumors in children in contrast to adults who typically have supratentorial lesions. The median time interval between symptom onset and tumor diagnosis is two months. Astrocytomas account for about 60 percent of pediatric brain tumors, and their biologic behavior differs from adult tumors. In children, five year survival rates may vary from 90 percent in cerebellar astrocytomas to less than 20 percent in brainstem gliomas.

Because of their location, brain tumors in children have unique features in their clinical presentation. Symptoms of increased intracranial pressure are fre-
BRAIN TUMORS IN CHILDREN; A REVIEW

quently seen with headaches and vomiting being the most conspicuous. Other non-specific symptoms and signs should be sought; these include changes in personality and school performance, lethargy, fluctuations in weight, and neuroendocrine problems. Early signs of papilledema, such as cecal scotomas and dyschromatopsia, may be present. Incipient tonsillar herniation may induce a head tilt or neck stiffness. Hemisensory, hemimotor, or hemianopic defects suggest a localization in the cerebral hemisphere, while the triad of long tract signs and ataxia in association with lethargy points to brain stem involvement. Radicular symptoms such as pain, weakness, or paresthesias that follow a dermatomal pattern suggest cerebrospinal fluid seeding by tumor cells and should prompt a search for the primary tumor and the extent of its dissemination.

Visual complaints in children with neurofibromatosis Type I may be symptoms of an optic nerve glioma; visual acuity and visual fields should be monitored carefully in these patients. Signs of neuroendocrine dysfunction such as fluctuations in growth and development suggest lesions in midline structures such as the hypothalamus and pineal gland.

Seizures are more frequently associated with slow growing tumors than with more aggressive lesions. Complex partial seizures are the most common seizure type seen with intracranial masses. Tumors in the temporal lobe usually cause seizures early in the course of disease.

**Pathology**

It is an axiom of pediatric neurology that in the first decade of life 50 percent of all brain tumors will be in the posterior fossa and will most frequently be of glial origin.

**Astrocytomas**

Astrocytomas in children are frequently of low grade. They are characterized by a feltwork of fibrillar processes. Pilocytic (figure 1), protoplasmic, microcystic (figure 2), and gemistocytic patterns are recognized. Occasional transformation to higher grade lesions, including glioblastomas, may occur. The recent Mayo Clinic classification is simple, precise, reproducible, and correlates histologic grade with probability of survival. Astrocytomas in children, even anaplastic tumors, generally have a better prognosis than adult tumors of comparable grade.

Cerebellar astrocytomas have the best prognosis of any childhood brain tumor. Lesions corresponding to the "Glioma A" of Gilles comprise two thirds of cerebellar astrocytomas and are characterized by microcysts, Rosenthal fibers, leptomeningeal deposits, and foci of oligodendroglioma. "Glioma B" has a poor prognosis and shares histologic features with ependymomas including perivascular pseudorosettes, mitosis, high cell density, and necrosis. Vascular endothelial proliferation and leptomeningeal invasion are sometimes seen in low grade cerebellar astrocytomas of children and do not have the ominous prognostic connotation that they carry in adult tumors. Ninety percent of 25-year survivals after surgery are reported in pediatric cerebellar astrocytomas. Rare malignant degeneration may be seen in association with neurofibromatosis.

**Ependymomas**

Ependymomas in children are usually found in the posterior fossa, often within the cavity of the fourth ventricle. Tumor cells have a pinpoint nuclear chromatin pattern and are typically arranged in a radial fashion to form
Figure 1. Juvenile pilocytic astrocytoma. Cerebellum. Many eosinophilic granular bodies and Rosenthal fibers are present. Tumor cells are bipolar with piloid cytoplasmic processes. Nuclear atypia is not indicative of poor prognosis. (H&E × 400)

Figure 2. Microcystic astrocytoma. Lateral cerebellum. Tumor nuclei are bland, and there is a delicate fibrillar background. Numerous microcysts contain a proteinaceous transudate. (H&E × 250)
BRAIN TUMORS IN CHILDREN; A REVIEW

rosettes or perivascular pseudoro-settes.\textsuperscript{18} Cilia and blepharoplasts may be present in the apical cytoplasm and when present help to confirm the diagnosis (figure 3). Ependymomas have an unfortunate tendency to metastasize throughout the cerebrospinal fluid pathways. Mitoses and other malignant features are seen in 50 percent of cases, usually in infants.\textsuperscript{41}

**Medulloblastomas**

Medulloblastomas are said to originate from the fetal granular cell layer of Obersteiner.\textsuperscript{47} By definition these tumors are exclusively cerebellar. They are found most often in the midline and constitute about 40 percent of all posterior fossa lesions.\textsuperscript{38} They are grossly soft, friable and often well demarcated tumors with occasional necrosis, cyst formation and calcification. Leptomeningeal and cerebrospinal fluid seeding occurs frequently. Extraneural metastases to lymph nodes and bone marrow may be seen.\textsuperscript{27} These tumors are characterized by their dense cellularity, frequent mitoses, and Homer Wright rosettes. A nodular or follicular growth pattern is sometimes encountered in medulloblastomas. Frequently, this pattern is the consequence of proliferation of desmoplastic elements within the tumor, or may indicate neuroblastic or glial differentiation within the tumor.\textsuperscript{26} Medulloblastomas once carried a dismal prognosis, but with the advancement in radiation and chemotherapy, five year survival can be as high as 70 percent.\textsuperscript{19} Polyamines may be useful tumor markers to monitor during the course of treatment.\textsuperscript{13}

**Primitive Neuroectodermal Tumors**

Tumors histologically and clinically similar to medulloblastomas are occa-

![Figure 3. Ependymoma. Fourth ventricle. Tumor cells form a characteristic rosette. Blepharoplasts are seen as densities in the apical cytoplasm. (H&E ×400)](image-url)
sionally seen in the cerebral hemispheres, and have been referred to by a variety of terms including “cerebral neuroblastomas”. Recently, it has become fashionable to refer to these poorly differentiated small cell neoplasms as “primitive neuroectodermal tumors” (PNET) (figure 4). This unifying concept suggests an origin of these lesions from undifferentiated neural cells and implies a mechanism of oncogenesis that is unproven. While this term (PNET) is widely and uncritically used, Scheithauer states: “Although it is a provocative concept, it does little to forward our understanding of neoplasia and it is a poor basis for a morphological system of tumor classification.”

Germ Cell Tumors

Germ cell tumors of the brain are rare but distinctly pediatric neoplasms. They account for about 15 percent of all brain tumors in children, but less than one percent of adult brain tumors. They are located in the midline either in the pineal region or less often in a suprasellar site. More often found in males, they are typically associated with developmental abnormalities and neuroendocrine disorders, especially precocious puberty. Histologically, these lesions resemble the germ cell tumors of the testis. The most frequent type is a germinoma. Mixed patterns with features of choriocarcinoma, embryonal carcinoma, endodermal sinus tumors, and teratomas with mature and immature elements are encountered (figure 5). Tumor markers including alpha-fetoprotein, human chorionic gonadotropin, and human placental lactogen may be elaborated by germ cell neoplasms. The identification of these markers in the blood and cerebrospinal fluid may facilitate diagnosis and treatment.

Figure 4. Primitive neuroectodermal tumor (PNET). Cerebral hemisphere. There is a nesting pattern of undifferentiated neuroepithelial cells. (H&E × 250)
Sarcomas

True, primary central nervous system sarcomas are rare, but they may be found in the first decade of life. Some arise from the meningeal coverings of the brain, but a certain number clearly originate from the cerebral parenchyma without any attachment to the arachnoid or dura.\textsuperscript{41} The polymorphic cell variant is the least differentiated type, has the most aggressive biology, and has a propensity to disseminate throughout the subarachnoid space. Primary rhabdomyosarcomas of the brain may be found in pure form or mixed with other mesenchymal elements.\textsuperscript{23}

Diagnosis

Several recent developments have enhanced the accuracy of brain tumor diagnosis. Computed tomography of the brain and nuclear magnetic resonance, along with the use of contrast material and paramagnetic agents, have enormously facilitated brain tumor diagnosis and provide fine anatomic detail.\textsuperscript{3,15} Oncogenes are genes that are inappropriately expressed and contribute to the development of neoplasia. More than 40 oncogenes have been identified. Of interest in pediatric neuro-oncology is the amplification of the N-myc oncogene in neuroblastoma. Survival with this tumor correlates inversely with the degree of amplification found.\textsuperscript{34} In five percent of non-inherited forms of retinoblastoma, a constitutional deletion of chromosomal band 13q14 has been observed. In familial cases, there is close genetic linkage between esterase D and the disease. Associations between C-myc and ERB-B oncogenes have been found with glioblastomas.\textsuperscript{46} The spreading availability of polymerase chain reaction technology may make molecular diagnosis routine in hospital laboratories.
Flow Cytometry

Flow cytometry is a powerful tool in the transition from descriptive to quantitative cytology. The presence of abnormal deoxyribonucleic acid (DNA) stem lines in solid tumors makes DNA flow cytometry a helpful modality in the diagnosis of bladder irrigates, effusions, sputum, bronchial washings, and cerebrospinal fluid collections. The adverse impact of aneuploidy and S percentage may make these useful prognostic parameters. Studies have documented higher rates of relapse in brain tumors found to be aneuploid, especially medulloblastomas.4

Immunohistochemistry and Tumor Markers

Immunohistochemistry and tumor markers have greatly strengthened the armamentarium of oncologists. Peroxidase-antiperoxidase techniques for the demonstration of neural and non-neural cell markers have contributed to diagnostic accuracy of histologically rare, complex or otherwise difficult tumors of the central nervous system.7 It is important to emphasize, however, that none of these markers is specific, and that each should be interpreted in the light of other clinical and laboratory information. Some tumor markers, such as polyamines, can be monitored during treatment to gauge disease progression or efficacy of therapy.13 In table I are presented some of the more useful markers available.

Electron Microscopy

Electron microscopy often makes a valuable contribution in identifying and classifying tumors that pose diagnostic problems. Electron microscopy can be especially decisive in the diagnosis of small cell tumors of the brain, poorly differentiated gliomas, unusual meningeal tumors, and anaplastic metastatic neoplasms.47 It may also help to distinguish metabolic diseases or viral and other infections that may be confused with tumors.

Treatment and Complications

Surgical resection, when feasible, radiation therapy, and chemotherapy remain the mainstays of treatment for brain tumors. Thirty percent of posterior fossa tumors require cerebrospinal fluid diversion via shunts. Total craniospinal radiation are required for tumors such as

<table>
<thead>
<tr>
<th>Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choroid plexus carcinoma</strong></td>
</tr>
<tr>
<td><strong>Pilocytic astrocytoma</strong></td>
</tr>
<tr>
<td><strong>Neuroblastoma</strong></td>
</tr>
<tr>
<td><strong>Medulloblastoma</strong></td>
</tr>
<tr>
<td><strong>Germ cell neoplasia</strong></td>
</tr>
<tr>
<td><strong>Meningeal carcinomatosis</strong></td>
</tr>
<tr>
<td>To differentiate metastasis</td>
</tr>
</tbody>
</table>

* CEA, a marker of secretory carcinomas, is routinely detected in choroid plexus carcinomas, but not in papillomas.

c Glial fibrillary acidic protein, intermediate filament, specific for the astrocytic series, either normal, reactive, or neoplastic. This protein was originally isolated from old multiple sclerosis plaques. Cancer 51:233-237, 1983.
d Human chorionic gonadotropin.
e Alpha-fetoprotein.
medulloblastomas and anaplastic ependymomas that seed the cerebrospinal fluid. Young children are more susceptible to radiation toxicity. The combination of methotrexate and radiation puts the brain at risk for the development of subacute necrotizing leukoencephalopathy (table II).

Acknowledgments

Appreciation is expressed by the authors to Jane Ryan for preparation of the manuscript.

References


<table>
<thead>
<tr>
<th>Modality</th>
<th>Side Effect</th>
<th>Time of Appearance</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT c, Methotrexate</td>
<td>Meningitic reaction</td>
<td>72 hours</td>
<td>Nuchal rigidity, nausea, headache, benign, self-limited</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Symmetrical polyneuropathy</td>
<td>2 weeks</td>
<td>Paresthesias, dropped ankle jerks</td>
</tr>
<tr>
<td>RT d (WBRT) e</td>
<td>Somnolence</td>
<td>1–2 months</td>
<td>Seen in 40% of children after prophylactic RTd for ALL f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lasts several weeks, relieved by steroids</td>
</tr>
<tr>
<td>RT d</td>
<td>Brain necrosis,</td>
<td>6 months to 3 years</td>
<td>Behaves clinically as tumor recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dorsal cord most vulnerable, paraparesis &amp; sphincter dysfunction</td>
</tr>
<tr>
<td>RT d</td>
<td>Myelopathy</td>
<td>12 months</td>
<td>Occurs in 1% of cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Highest incidence if age is less than 13 or dose more than 3,000 rads</td>
</tr>
<tr>
<td>RT d</td>
<td>Secondary cancer</td>
<td>After 7 years</td>
<td>Worse if age is less than 3 at time of treatment</td>
</tr>
<tr>
<td></td>
<td>Endocrine, decrease GH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT d</td>
<td>Intellectual impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT d</td>
<td>Premature arteriosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT d and chemotherapy</td>
<td>Atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b Cancer 5:233–237, 1983  
c Intrathecal  
d Radiation therapy  
e Whole brain radiation therapy  
f Acute lymphoblastic leukemia  
g Growth hormone


