A series of 18 primitive neuroectodermal tumors in children (15 cerebral and three spinal) is reported. These are highly malignant neoplasms, both histologically and clinically. They are rapidly growing tumors, with a brief duration of symptoms and a rapidly progressive course. Forty percent of the patients were alive at 6 months, only 10% at 1 year, and all patients had died within 2 years following diagnosis.

**Key Words**  
- primitive neuroectodermal tumor  
- brain neoplasm  
- spinal cord neoplasm  
- central neuroblastoma

In children, we have occasionally encountered highly cellular, primitive central nervous system (CNS) neoplasms that are difficult to classify. Such primitive neuroectodermal neoplasms most frequently arise in the cerebellum of children, and have traditionally been termed medulloblastomas. Histologically similar neoplasms originate less frequently in unusual sites such as the cerebral hemispheres or spinal cord.

The cerebral examples of this type have been most often designated cerebral or central neuroblastomas, a term which we believe is too restrictive in view of their variable yet frequent glial as well as neuronal differentiation. The term “primitive neuroectodermal tumors” (PNET’s) as used by Hart and Earle more accurately expresses the characteristics of this group.

This report describes 15 cerebral and three spinal PNET’s seen at Children’s Hospital, Columbus, Ohio. The primitive neoplasms of the posterior fossa, that is, medulloblastomas, similar neoplasms of presumed pineal origin (pineoblastomas), and peripheral neuroblastomas, have not been included in this series.

**Summary of Cases**

**Clinical Data**

The average age of the patients in this series was 3.1 years. The oldest patient was aged 10 years and the youngest 6 months. There was no apparent sex predilection, with 10 females and eight males.

These are rapidly growing neoplasms as seen by the extremely short duration of symptoms, which averaged about 3 weeks when the one patient with a long history is omitted. This patient presented with a long history of seizures and more recent decompensation in her neurological status. Eight patients presented with headache, nine with nausea and vomiting, and three with lethargy. Motor signs, namely, hemiparesis and paraparesis, were presenting problems in eight of these patients. Seizures were noted in five children, papilledema in four. Anorexia was seen in two cases; both of these children had anterior third ventricular lesions.

Three patients had frontal lesions, three temporal, three parietal, two occipital, and four in the region of the third ventricle. Three tumors were seen in the spinal cord: two in...
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Figure 1. Survival data in 12 cases of primitive neuroectodermal tumors.

The cervical and one in the thoracolumbar spine. These latter tumors were believed to be primary spinal cord lesions, as neither cerebral nor cerebellar intra-axial lesions, nor peripheral neuroblastomas were seen. This was verified by autopsy in two cases.

Diagnostic Evaluation

Skull films demonstrated split sutures in most of the cerebral cases, and spine films revealed widened pedicles in all three spinal cases. Electroencephalography demonstrated diffuse slowing with focal delta change over the area of tumor in several of these children. Nuclear brain scan was positive in all cases of cerebral tumors, at times suggestive of cystic lesion. Angiography, ventriculography, and myelography were performed. Computerized tomography (CT) should be most helpful in evaluation of these lesions. Only our most recent case had a CT scan performed.

Treatment

All of these patients underwent surgical therapy. The preoperative diagnosis of cerebral abscess led to an initial aspiration in several cases. Subtotal resection was performed, with lobectomy and ventriculolu- jugular shunting on several occasions. Decompressive laminectomy was carried out in all three spinal cases.

Radiation therapy in the range of 4000 to 6000 rads was given to each child with the exception of one child who died 1 month postoperatively. Chemotherapy included in the past intrathecal methotrexate and presently a combination of vincristine, prednisone, and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).

Survival Data

As expected in rapidly growing tumors such as these, the survival in this series was poor. Adequate follow-up data were available in 12 cases. Less than 40% of these patients were alive 6 months after diagnosis, less than 10% at 1 year (Fig. 1).

Pathology

Gross Appearance. The two most distinctive gross features of the cerebral neoplasms are their frequent appearance of sharp margins and the presence of a necrotic, cystic-appearing center (Fig. 2). Gross cystic change was found in five of our cases. Several surgical specimens resembled brain abscesses, and only a biopsy of the viable tumor in the wall was diagnostic.

Due to their apparent sharp delineation from the adjacent brain tissue, and the central necrosis, these tumors often grossly suggested metastatic tumors. The problem of differential diagnosis was compounded by the histological appearance of sheets of apparently undifferentiated cells. However, intraparenchymal CNS metastases are rare in young children. Focal areas of the neoplasm usually exhibit the more typical neuroectodermal appearance. No extra-axial primary tumors were evident in any of these patients.

Figure 2. A left temporal lobe primitive neuroectodermal tumor in a child who survived 5 months following craniotomy with subtotal resection and subsequent irradiation and chemotherapy. Note the pronounced shift of the midline structures.
Primitive neuroectodermal tumors in children

**Microscopic Appearance.** All of these PNET's shared a histological appearance reminiscent of the germinal matrix tissue of the developing brain. They had a high cell density and the slide stained with hematoxylin and eosin was usually grossly basophilic due to the nuclear density. These tumors have been referred to as "blue tumors." Most of the individual cells lacked much evidence of differentiation. Focal areas or cells showing differentiation were frequently present.

The poorly differentiated areas contained cells with little or no evident cytoplasm and moderate-sized nuclei which occasionally contained prominent nucleoli. Several cases contained focal pleomorphic giant cells. In several of our cases there were epithelial-like sheets of poorly differentiated cells with visible cytoplasm and prominent nucleoli. These areas were reminiscent of germ cell neoplasms. Mitotic figures were numerous in the poorly differentiated areas. Areas of necrosis and vascular endothelial hyperplasia were usually present. The histological malignancy of these neoplasms was obvious, and rapid growth of the neoplasm may have caused both the central necrosis and the circumscribed, "pushing" margins.

Differentiation in our cases was quite variable. The earliest evidence of neuronal differentiation was equivocal (Fig. 3) and consisted of increases in cellular size and in prominence of cytoplasm, and especially prominence of a nucleolus in a relatively vesicular nucleus. Homer-Wright rosettes with central fibrillary tangles were regarded as more evidence of early neuronal differentiation. Well differentiated yet neoplastic neurons were not seen in our material.

Focal glial differentiation was seen in most of these neoplasms, and was indicated by increase in cell size and formation of glial processes. Early glial differentiation was evident in some cases in which the cells were elongated and assumed a spongioblastic appearance. Delicate, fibrillary, material positive to phosphotungstic acid hematoxylin (PTAH) was often evident in more advanced glial differentiation (Fig. 4). Slightly more than one-half of the cases which were stained by the PTAH technique showed evidence of glial differentiation.
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FIG. 5. Area of oligodendrogiial differentiation in a neoplasm that had undifferentiated areas, as well as areas of astrocytic appearance. Masson trichrome, × 360.

FIG. 6. Prominent connective tissue septae between clusters of highly cellular neoplasm. Masson trichrome, × 100.

FIG. 7. Sections of thoracic and lumbosacral spinal cord. Neoplasm surrounds and involves the spinal cord. The extradural space is not involved at this level, but there was focal extradural extension. Metastases were present in an esophageal lymph node, bone, and lung (subpleural).

Occasionally a pattern of perivascular pseudorosettes (ependymal differentiation) or sheets of cells resembling oligodendroglioma (Fig. 5) were observed. A prominent mesenchymal component (Fig. 6) was present in nine or 50% of our cases. Mesenchymal components in the form of striated muscle have been reported in medulloblastoma and intracocular medulloepitheliomas. The origin (reactive or neoplastic) and significance of mesenchymal components in PNET's is unclear, but abundant connective tissue is a frequent feature of various primitive neuroectodermal tumors.

The gross circumscribed appearance was deceptive, since there were usually microscopic islands of perivascular or parenchymal invasion even in the initial biopsy. Spread within the CNS was seen in all of our
Primitive neuroectodermal tumors in children

Fig. 8. Relationships of primitive neuroectodermal tumors, and other neoplasms of the central nervous system.

six autopsied cases, particularly subarachnoid invasion, but ventricular spread was also seen in two of the six autopsy cases. One of our patients, with a primary spinal cord tumor (Fig. 7), had distant metastases (lung, bone marrow, and lymph node) as well as extensive subarachnoid and ventricular spread in the CNS. This case is similar to a metastasizing spinal cord tumor in the series reported by Smith, et al. In view of the morphological similarity to medulloblastomas, it is important in such cases to rule out a primary medulloblastoma with secondary spinal or cerebral invasion.

Discussion

Histologically these neoplasms are similar or identical to medulloblastomas or PNET's of other sites (pineoblastoma, peripheral neuroblastoma) (Fig. 8).

The historical definition of medulloblastoma as a primitive cerebellar neoplasm and the relative frequency of this entity have justified a separate designation. However, even the medulloblastomas are quite variable in terms of degree and type of differentiation (glial or neuronal), and also in microscopic appearance. The medulloblastoma shares the histological malignancy, primitive character, and variable differentiation (neuronal, astrocytic, spongioblastic, or even oligodendrogial) with cerebral or spinal PNET's. The clinical behavior of the latter is also characteristic of other PNET's in terms of spread within, and occasionally outside, the CNS.

Medulloepithelioma is a rare primitive CNS neoplasm. In addition to the sheets of poorly differentiated cells, it is characterized by primitive tubular structures resembling the medullary epithelium, and has been well defined clinically and pathologically. Polar spongioblastoma is likewise a rare neoplasm with primitive features and a unique palisading pattern of elongated or “polar” cells that resemble the embryonic spongioblasts.

Cerebral PNET's merge imperceptibly as a spectrum with neoplasms which are classified according to their predominant cell type as tumors such as astrocytoma, ependymoma, mixed gliomas. Obviously many borderline cases are controversial. Features that distinguish these neoplasms from anaplastic glioma include the abrupt transition to adjacent brain. In spite of this, islands of microscopic perivascular invasion are usually seen. A prominent mesenchymal stroma and areas of differentiation along neuronal lines with predominance of poorly differentiated elements are further evidence against a pure, high-grade glioma.

Perivascular pseudorosettes are present in many of these cases but they rarely constitute the dominant histological pattern. We realize that some neuropathologists may prefer to designate such tumors as ependymoblastomas or malignant cellular ependymomas. However, the term ependymoblastoma has no clear or universal definition, and evidence of ependymal origin in many of these poorly differentiated tumors is slight. Regardless of their predominant histological type, their histological features and clinical behavior are similar to other PNET's.

Mixed gliomas are similar in some ways to PNET's. Although they are purely glial and lack the extremely primitive components, there is no clear dividing line between mixed
gliomas with poorly differentiated areas, and PNET's with glial differentiation. We follow the practice of Hart and Earle<sup>5</sup> and refer to tumors as PNET's when they are at least 90% undifferentiated. Another interface occurs with teratomas or teratoid tumors. These may also contain primitive neuroepithelial components<sup>12</sup> but should be excluded from the PNET group, even when they arise in the CNS.

There remains a group of cerebral neoplasms which contain mixtures of mature neurons and glial cells (gangliogliomas), mature neurons, and Schwann cells (ganglioneuromas), or which consist purely of neuronal elements with variable differentiation (gangliocytoma, ganglioneuroblastoma, or neuroblastoma).<sup>9</sup> These terms appear to be justified in certain cases. However, the neoplasms we reported did not fit precisely into any of these categories.

The exact degree of differentiation in PNET's is variable within areas of any given tumor and in different tumors. In fact, these neoplasms may be even less differentiated than the term "neuroectodermal" implies, since they may contain mesenchyme and/or primitive germ-type cells. However, they originate within the CNS, and, as expected, the neuroectodermal component is predominant. They have many clinicopathological features in common. They have similar behavior including the tendency to CNS dissemination<sup>14</sup> and extra-CNS spread. Thus, they should be classified together with medulloblastomas and pineoblastomas as primitive neuroectodermal tumors.

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References


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