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Primary Cerebral Neuroblastoma:
CT and MR Findings in 12 Cases

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A retrospective CT, MR, and clinical study was performed in 12 patients, five children and seven adults, with histologically proved primary CNS neuroblastoma. The CT and MR appearances of this neoplasia were more variable than generally recognized. Although seven tumors were predominantly intraparenchymal masses with calcification and cyst formation, five were intra- or juxtaventricular. CT was preferable to noncontrast MR both at initial diagnosis and follow-up for identification of calcification, recurrent tumor at surgical sites, and leptomeningeal disease. Noncontrast MR was useful primarily for localization of peri- and intraventricular lesions.

We conclude that primary CNS neuroblastoma has a more variable radiographic appearance than is generally recognized, and that an intra- or periventricular epicenter is common.

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Primary cerebral neuroblastoma is a rare neoplasm typically described in children as a large intraparenchymal supratentorial mass frequently containing cysts, calcification, and spontaneous hemorrhage [1–10]. This tumor is generally considered to be a specific subset of primitive neuroectodermal tumors, although neuropathologic controversy exists. Detailed electron microscopy may be required for the exact diagnosis. These tumors are malignant lesions with a high rate of recurrence after therapy and frequent subarachnoid metastases. Our experience indicates that primary CNS neuroblastoma has a broader spectrum in presentation, age of onset, location, and radiographic appearance than is generally recognized. We report our experience with primary cerebral neuroblastoma in 12 patients and describe its CT and MR characteristics with clinical, surgical, and histological correlation.

Materials and Methods

From August 1979 to August 1988, 12 patients (six females, six males) with primary cerebral neuroblastomas were identified. Those with ganglioneuromas, esthesioneuroblastomas, or metastatic neuroblastomas from an extracranial primary had been excluded from the present study. The study group comprised five children 15 days to 9 years old and seven adults 19–52 years old. All tumors were histologically proved (one by CT-directed brain biopsy, one by open biopsy, and 10 by surgical resection). All surgical resections were reported as subtotal with removal of 50–95% of the tumor. Three adult patients have been reported previously [11, 12].

Pathologic criteria used in this study for diagnosis of primary cerebral neuroblastoma included identification of a cellular tumor comprising small hyperchromatic cells in a fine fibrillary background with occasional Homer-Wright rosettes. Ultrastructurally, these tumors have neural process formation with intracytoplasmic microtubules and dense core granules [6–8]. Occasionally, synaptic formations are present (Fig. 1) [11–15].

A retrospective chart review made note of presenting signs and symptoms, tumor location, mode of tumor spread, therapies used, and progression of disease. These findings are summarized in Table 1.

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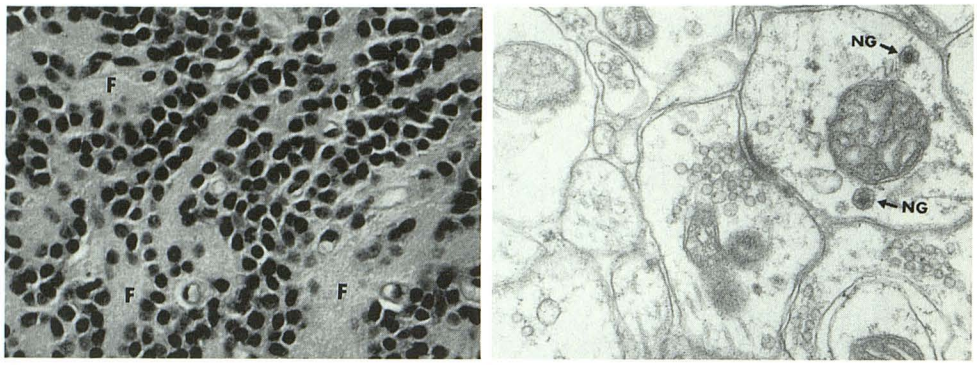

Fig. 1.—*A*, Case 3: Small cells are arranged within fine fibrillary background (F). In this field, neuroepithelial character of tumor is well maintained. (H and E, ×500)

***B*, Case 2. Well-formed synapse (center) and neurosecretory granules (NG) are ultrastructural features of well-differentiated neuronal neoplasm. (Electron microscopy, ×24,500)**

TABLE 1: Profile of Patients with Primary Cerebral Neuroblastomas

Case No.	Age	Sex	Presenting Symptoms and Signs	Location	CSF Seeding	Follow-up	Therapy
1	32	F	Seizures, R arm weakness	L frontal & temporal	–	Deceased 2 d postop	Surgery
2	20	F	Ataxia, increased intracranial pressure, R arm hyperesthesia	L lateral ventricle	–	Progressive mass effect; ?radiation necrosis (3¾ yr)	Surgery, radiation
3	23	M	Headaches & decreased vision, OS; von Hippel–Lindau disease	L lateral ventricle	–	Stable with residual tumor (6½ yr)	Surgery, radiation
4	52	F	Dizziness, incoordination, R hyperreflexia	L lateral ventricle	Positive CSF cytology (3 yr)	Residual tumor (3 yr)	Surgery, radiation
5	34	M	Increased intracranial pressure, R hemiparesis	L frontal lobe	–	Extensive recurrence, terminal (1¼ yr)	Surgery, radiation
6	4	F	Increased intracranial pressure, stiff neck	R frontal & parietal	Spinal & cranial seeding (2½ yr)	Deceased (2½ yr)	Surgery, radiation, & chemotherapy
7	1	M	Seizures, gait disorder	L parietal	–	Stable (3 yr); no recurrence, no residual tumor	Surgery, chemotherapy
8	2	M	L hemiparesis, macrocephaly	R frontal & temporal	–	Residual tumor; stable (2¼ yr)	Surgery, chemotherapy, radiation
9	19	M	Increased intracranial pressure, gait difficulty	Third ventricle	–	Lost to follow-up (7 wk)	CT biopsy
10	9	M	Increased intracranial pressure	All ventricles with subarachnoid seeding	At time of diagnosis & recurrence of spinal & periventricular seeding (2¾ yr)	Deceased (2¾ yr)	Biopsy, radiation, & chemotherapy
11	29	F	Seizures	R frontal lobe & R lateral ventricle	Nodule, R lateral ventricle, at diagnosis	Stable with residual tumor (6 mo)	Surgery, radiation, & chemotherapy
12	2 wk	F	Vomiting, macrocephaly	R temporal, occipital, and parietal	–	Stable with marked developmental delay (2½ yr)	Surgery, chemotherapy

Note.—R = right; L = left; OS = left eye.

All patients had CT scans before and after therapeutic intervention. Axial CT scans with IV contrast material and 4- to 10-mm collimation were completed preoperatively in all patients. In addition, seven patients had noncontrast CT. One patient died 2 days after surgical resection and one was lost to follow-up 7 weeks after diagnosis. Mean follow-up was 2.3 years (range, 2 days to 6½ years). Four patients died during the period of study, with a mean survival from time of diagnosis in these patients of 1.4 years (range, 2 days to 2¾ years).

Three patients had MR examinations before therapy and five patients had follow-up MR examinations. MR examinations were performed with a 0.5-T superconducting magnet (Philips Gyroscan) using a standard head coil (23 cm). MR examinations were completed with T1-weighted, 500–750/30–50 (TR/TE), or inversion-recovery, 1700/700/30 (TR/TI/TE), and double-echo T2-weighted, 2000–2215/30,60 or 2000–2215/50,100, techniques. Axial-plane imaging with 10-mm slices was initially performed with subsequent coronal and/or sagittal images based on the location of pathology encountered. IV

gadolinium-DTPA (0.1 mg/kg, Berlex, Inc.) studies were performed in two patients: one during a a phase III drug evaluation after informed consent was obtained and one after Food and Drug Administration approval.

CT and MR examinations performed before, during, and after therapy were evaluated for tumor size, epicenter, proximity to the ventricular system, and tumor characteristics (edema, mass effect/hydrocephalus, hemorrhage, calcifications, cyst formation, seeding, response to therapy, and sequelae of therapy).

Results

Clinical data, location of tumor, therapy administered, and duration of follow-up are summarized in Table 1.

The "typical" CT imaging appearance previously reported for primary neuroblastoma [1–5]—a large intraparenchymal calcified and cystic mass often with spontaneous hemorrhage and little edema relative to the size of the lesion—was encountered in seven patients (three children, four adults; Fig. 2). These tumors were approximately 3–10 cm in diameter. In four cases the epicenter of the tumor was intraparenchymal but the tumor extended medially to abut the lateral ventricular margin.

With CT, two tumors contained calcifications, three hemorrhaged spontaneously, and two resulted in hydrocephalus. After IV contrast enhancement, these masses enhanced inhomogeneously. One patient with a primary neuroblastoma of the frontal lobe near a site of meningioma resection 11 years before had a focal subependymal metastasis at the time of diagnosis. Cystic-appearing areas were apparent in six patients and mild peritumoral edema in two.

Preoperative MR in two patients revealed an intraparenchymal mass with inhomogeneous intensity patterns on both T1- and T2-weighted studies. Differentiation among dense calcification, flow void, and hemosiderin was difficult with MR. Smaller and less dense calcifications were not recognized. Cystic areas seen on CT were difficult to distinguish from the remainder of the tumor on MR. Mild peritumoral edema was present in one patient. Spontaneous hemorrhage resulted in intratumoral and intraventricular regions of high signal intensity, presumably due to methemoglobin on T1-weighted studies (case 6, Fig. 2).

Five patients (two children, three adults) had primary tumors with an intra- and/or periventricular epicenter, and four had secondary hydrocephalus. Tumor size was difficult to assess in this group, but was estimated as 1–6 cm in maximum diameter.

On CT, four masses contained calcification, one had extensive subarachnoid seeding at presentation (Fig. 3), and none hemorrhaged spontaneously. Enhancement after IV contrast administration occurred on CT in all cases.

Preoperative MR was useful for better localization of intraventricular tumor with sagittal and coronal imaging; however, areas of low signal intensity from calcification, flow void, and prior hemorrhage were indistinguishable. T1-weighted gadolinium follow-up studies in two patients resulted in greater contrast between tumor and normal brain (Fig. 4).

A brief profile of therapy and disease progress is given in Table 1. Of the seven patients with typical intraparenchymal lesions, one was stable without evidence of recurrent or residual tumor. The others had residual and/or recurrent tumor. In this group, as expected, neoplasia was better differentiated from postsurgical gliosis and cysts/necrosis (Fig. 5) with contrast-enhanced CT than with noncontrast MR. In one patient who developed leptomeningeal seeding, contrast-enhanced CT revealed more intracranial disease than MR did; however, MR noninvasively revealed characteristic lesions of spinal seeding (Figs. 2E and 2F).

Of the five patients with intra- and periventricular lesions, one was lost to follow-up after 7 weeks; one initially responded well to radiation therapy, but subsequently succumbed to recurrent leptomeningeal disease; one had progressive edema thought to represent radiation necrosis; and two were stable with residual tumor (two patients) and leptomeningeal seeding (one patient).

Tumor size and location were the predominant factors influencing surgical resectability. No significant differences were apparent in adults compared with children in survival or tumor aggressiveness in this small series. No distant metastases or extension outside the CNS were documented.

Discussion

Primary CNS neuroblastoma often is considered a subset of primitive neuroectodermal tumors, although this categorization is controversial. Russell and Rubinstein [15] suggest that this classification is misleading since it combines a histologically inhomogeneous group of tumors as if they were pathologically indistinguishable. This broad classification was suggested in 1973 [16] as a descriptive term for predominantly undifferentiated, or at times undiagnosed supratentorial tumors in children, which microscopically (without electron microscopy) were thought to originate from the primitive neural tube. These were malignant, often cystic, compressed adjacent brain, and could exhibit foci of glial and/or neuronal differentiation. The primitive neuroectodermal tumor group includes medulloblastoma, medulloepithelioma, neuroblastoma, spongioblastoma, ependymoblastoma, and pineoblastoma [14]. Horten and Rubinstein [6], however, suggested that primary cerebral neuroblastoma is a nosologic entity distinct from primitive neuroectodermal tumors and characterized by (1) a cellular tumor of neuronal origin, without glial differentiation; (2) the presence of a fine fibrillary matrix of axonal material; (3) occasional differentiation to mature ganglion cells; and (4) the frequent exhibition of well-formed Homer-Wright rosettes. On electron microscopy, recognition of neurosecretory granules allows a precise diagnosis [17].

Previously published radiologic studies describe the typical primary CNS neuroblastoma as an intraparenchymal, supratentorial mass with little associated edema occurring in a child. Calcification, cyst formation, and spontaneous hemorrhage are common at presentation [1–5], and subarachnoid tumor seeding is a frequent sequela.

In our series, the age of onset and radiologic appearances of the lesion were more variable than previously recognized: A periventricular and/or intraventricular epicenter was common both in children and in adults, occurring in five of 12 patients. In addition, four of seven tumors that were predominantly intraparenchymal abutted a ventricular margin. Spon-

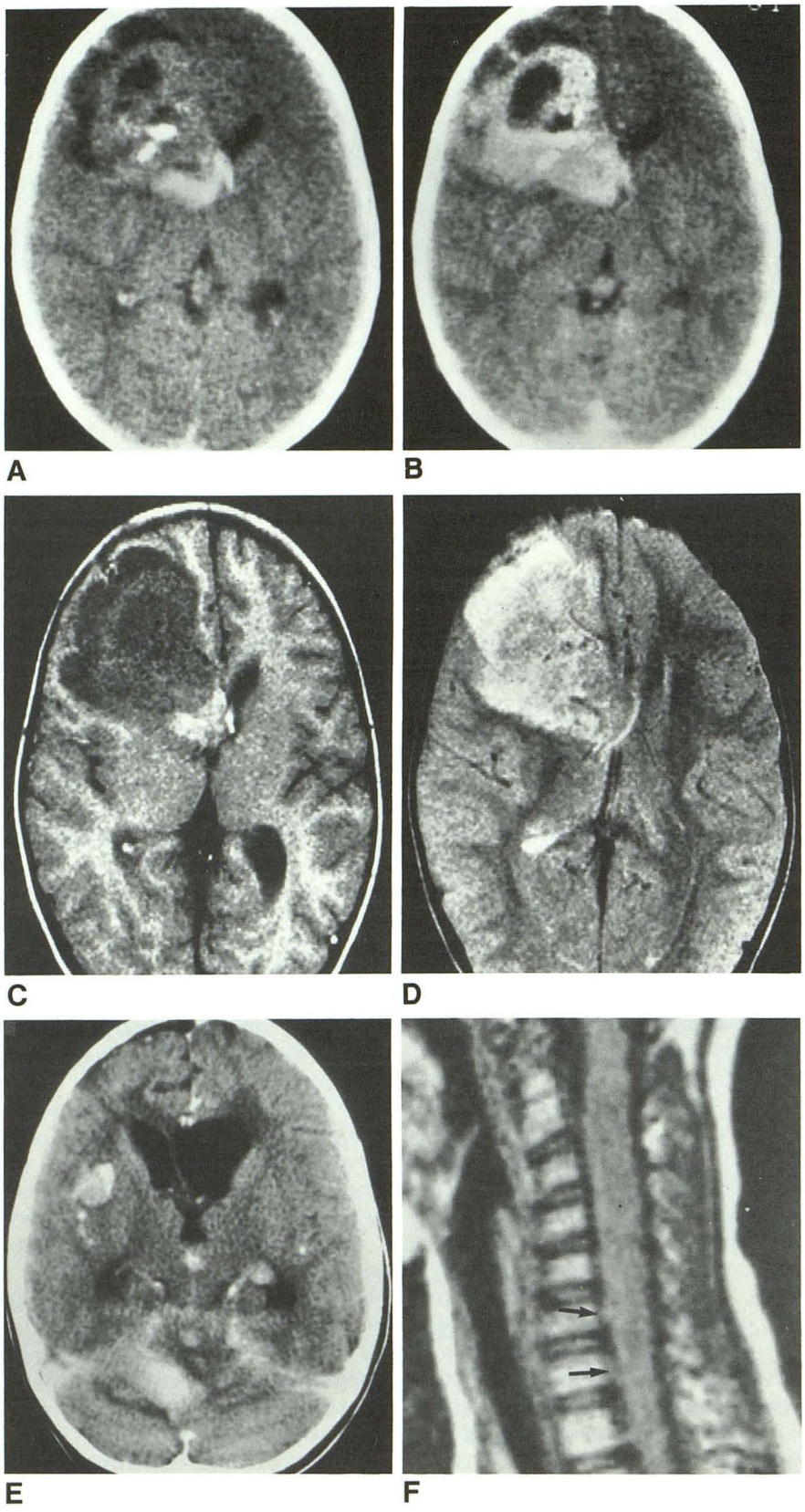

Fig. 2.—Case 6: Primary CNS neuroblastoma in 4-year-old girl with spontaneous intratumoral and intraventricular hemorrhage.

A, Nonenhanced CT scan shows intratumoral calcifications and cyst formation with hematoma at foramen of Munro.

B, Contrast-enhanced CT scan shows marked tumor enhancement with relatively little adjacent edema.

C, T1-weighted MR image, 500/30 (0.5 T), shows primarily hypodense inhomogeneous tumor with increased signal intensity in hematoma adjacent to foramen of Munro.

D, Proton-density-weighted MR image, 2000/30, shows predominantly increased signal intensity throughout lesion with focal curvilinear areas of hypointensity corresponding to calcifications seen on nonenhanced CT.

E, 2½ years after extensive surgical resection, radiation, and chemotherapy, substantial nausea, vomiting, and headache developed abruptly, followed by coma. Contrast-enhanced CT scan shows leptomeningeal seeding.

F, Cervical-spine MR image, 500/30 (0.5 T), shows poorly defined nodules in subarachnoid space (*arrows*) compatible with seeding. In addition, irregularly enlarged cervical spinal cord suggests seeding on cord surface.

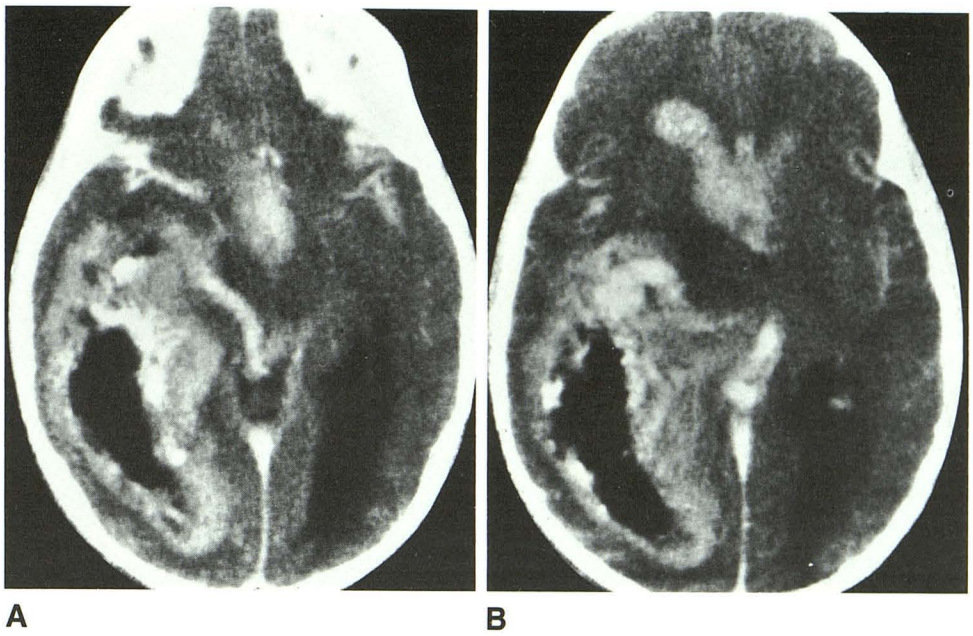

Fig. 3.—Case 10: 9-year-old boy.
A and *B*, Adjacent contrast-enhanced CT scans at presentation reveal marked enhancing and calcified periventricular neoplasia with subarachnoid seeding. No hemorrhage was recognized clinically or on nonenhanced CT.

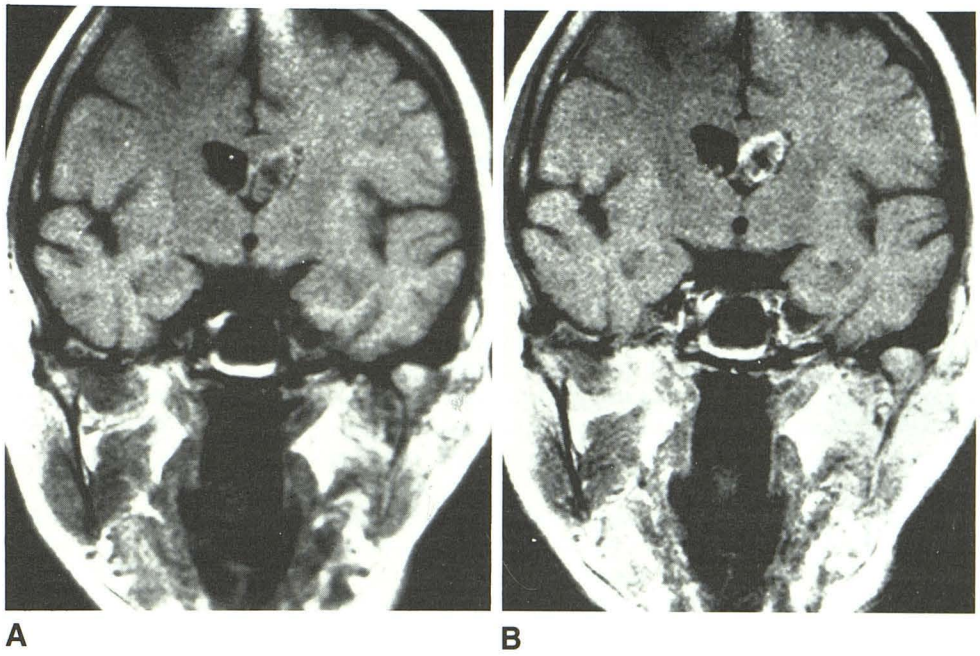

Fig. 4.—Case 4: 52-year-old woman.
A and *B*, Pre- (*A*) and post- (*B*) gadolinium-DTPA MR images, 550/30 (0.5 T), reveal peripheral enhancement of intraventricular primary CNS neuroblastoma.

taneous hemorrhage occurred only in predominantly intraparenchymal masses, but this may be a reflection of sample size. Misdiagnoses were common preoperatively, owing to the nonspecific CT and MR appearances and, perhaps, to the rarity of this tumor. Differential diagnoses considered in our cases included oligodendroglioma, astrocytoma, meningioma, ependymoma, and other primitive neuroectodermal tumors.

Pre- and postcontrast CT was the best available imaging technique for preoperative evaluation and follow-up of these lesions during this study. Calcifications were seen better on CT than on standard MR pulse sequences, and subarachnoid and periventricular seeding were inconspicuous on noncontrast MR. Contrast enhancement was essential for detection of subtle tumor recurrence around cystic masses; these areas of recurrence were not detectable on noncontrast MR. Gadolinium-enhanced MR and contrast-enhanced CT both demonstrate areas of blood-brain barrier disruption from tumor progression, although with either technique there is the potential for radiation necrosis, postsurgical enhancement, or superimposed infection to mimic tumor recurrence.

Noncontrast MR was not essential, and was primarily used as an ancillary technique for multiplanar localization of peri- and intraventricular lesions. Superficial and/or cortical masses were visible without artifact from the adjacent calvarium, but areas of abnormal signal intensity due to prior surgery and/or radiation therapy mimicked recurrent or residual neoplasia.

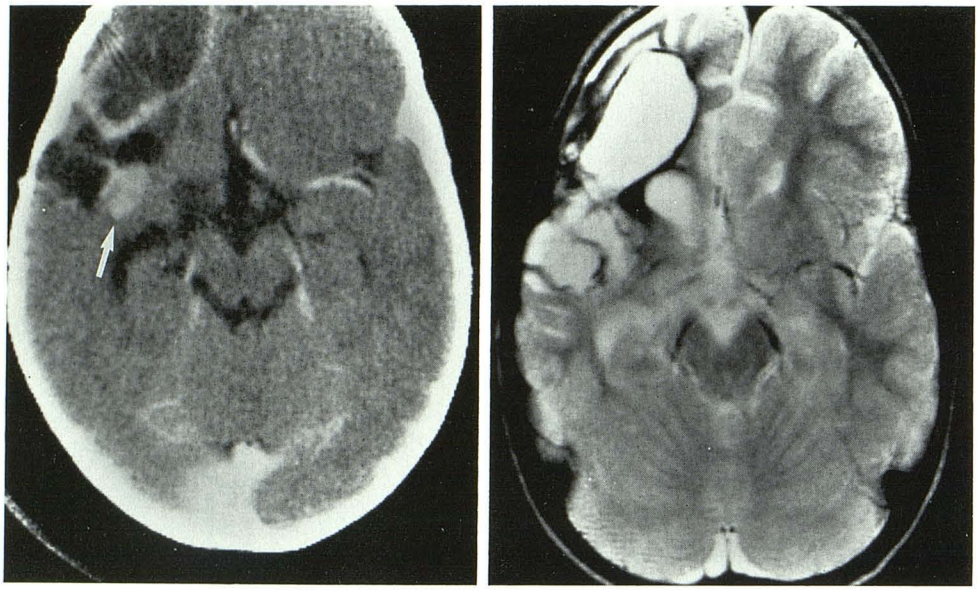

Fig. 5.—Case 8: 2-year-old boy with prior surgical resection.

***A*, Residual tumor adjacent to cyst (*arrow*) is seen on contrast-enhanced CT scan.**

***B*, MR image, 2000/100 (0.5 T), 3 months later. Residual tumor and cyst are difficult to differentiate. Subsequent contrast-enhanced CT revealed shrinkage of enhancing mass indicative of response to interval chemotherapy.**

MR contrast agents were not widely available during this study, particularly for children, but they have been shown to improve the accuracy of MR for leptomeningeal and recurrent tumors [18–20] and for evaluation of postoperative sites.

In summary, the CT and MR appearances of primary cerebral neuroblastoma are more variable than previously recognized. In our series, peri- and intraventricular lesions were frequent. CT was preferable to noncontrast MR both at initial diagnosis and on follow-up of these lesions owing to its sensitivity in demonstrating calcification and leptomeningeal disease. Contrast-enhanced CT was superior to noncontrast MR for differentiation of recurrent and residual neoplasia from sequelae of therapy, although, potentially, postsurgical enhancement or radiation necrosis might have a similar appearance. Multiplanar MR imaging was helpful primarily for localization of peri- and intraventricular lesions; MR contrast agents were essential for revealing tumor recurrence around cysts and at surgical sites and for leptomeningeal seeding. Primary CNS neuroblastoma has no pathognomonic appearance on CT or MR; thus, it should be considered in the differential diagnosis of intraparenchymal or juxtaventricular masses. Our experience has been that histopathological confirmation is required for definitive diagnosis. Primary cerebral neuroblastoma is an aggressive tumor with a relatively poor prognosis owing to local tumor recurrence and leptomeningeal seeding.

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