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*AJNR Am J Neuroradiol* 1982, 3 (6) 623-630

<http://www.ajnr.org/content/3/6/623>

This information is current as of September 7, 2025.

## Special Article

# Neuroblastoma Presenting as Central Nervous System Disease

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Neuroblastoma may be extremely difficult to recognize, particularly when the tumor presents as a primary central nervous system disease. Central nervous system involvement may be considered as primary intracerebral neuroblastoma, metastases to the cranium from an occult primary, primary intraorbital neuroblastoma originating in the ciliary ganglion, metastatic intraorbital neuroblastoma from an occult primary, primary intraspinal neuroblastoma originating in dorsal root ganglia, intraspinal metastatic disease, and distant effects such as myoclonic encephalopathy. Primary neuroblastoma within the ciliary ganglion and primary intraspinal neuroblastoma are extremely rare entities. Illustrative cases that demonstrate the broad spectrum of neurologic presentations are offered. The second known report of neuroblastoma in association with primary pulmonary hypoventilation (Ondine curse) is included.

The recognition of neuroblastoma may be difficult due to its diverse manifestations. Indicative of such difficulty is the term applied to this neoplasm, "the great imitator" [1]. While many patients present with constitutional symptoms such as nausea, vomiting, and irritability [1] and have an abdominal, pelvic, or retroperitoneal mass that contains characteristic punctate calcifications [2], the neoplasm may be extremely subtle in others, requiring extensive high-quality radiographic examinations for diagnosis. Adding to the difficulty is the fact that some patients have only neurologic signs and symptoms such as nausea, vomiting, and papilledema suggesting increased intracranial pressure; focal motor weakness; impaired vision and/or oculomotor function; ataxia, tremor, and opsoclonus (myoclonic encephalopathy) suggesting cerebellar disease; and paraparesis, with or without bowel and bladder dysfunction. Each of these neurologic presentations due to neuroblastoma suggests the possibility of primary neurologic disease. Preoperative consideration of neuroblastoma depends on an awareness of such neurologic presentations and appropriate diagnostic examinations.

We have assembled representative cases that illustrate many aspects of either primary or secondary neuroblastoma affecting the central nervous system (CNS). All of the patients had neurologic symptoms without known tumor elsewhere in the body. If the neurologic lesion later proved to be metastatic, the primary site was occult at the time of presentation. The signs, symptoms, and radiographic features at presentation are emphasized rather than the more classical findings present late in the disease process.

Seven major categories of neurologic involvement are represented: primary intracerebral neuroblastoma, metastatic disease to the cranium from an occult primary, primary intraorbital neuroblastoma, metastases to the orbit from an occult primary, primary intraspinal neuroblastoma, intraspinal metastatic disease, and neurologic effects from a distant tumor such as myoclonic encephalopathy. The classical clinical and radiographic findings of neuroblastoma seen in various parts of the body are covered. Then, a relevant case, differential diagnosis of the

Received September 11, 1981; accepted after revision July 9, 1982.

Presented at the annual meeting of the Radiological Society of North America, Chicago, November 1981.

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*AJNR* 3:623-630, November/December 1982  
0195-6108/82/0306-0623 \$00.00  
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radiographic and clinical findings at presentation, and the pathophysiology of neuroblastoma in that area are discussed.

### Classical Clinical and Radiographic Findings

The clinical and radiographic features of the common sites of involvement by neuroblastoma have been extensively described. Between 55% and 70% of neuroblastomas begin in the retroperitoneal region, with plain films of the abdomen or an excretory urogram demonstrating a suprarenal mass frequently containing punctate areas of calcification [2-6]. Plain films of the chest may likewise show a posterior mediastinal mass containing calcium [7]. A mass may also present in the neck along the cervical sympathetic chain.

Metastases are present in up to 70% of patients at the time of tumor detection [3], with metastatic tumor to bony structures being a very common finding. These bony metastases are characterized by multiple poorly marginated lytic zones and areas of irregular mottling [3, 6, 8]. Not only may such lytic areas be seen in the skull, but long-standing metastasis in the skull with extension into the scalp produces a "hair-on-end" appearance [2, 6, 8-11]. Extension intracranially produces epidural masses, with the dural boundary almost always respected. Extension of the epidural deposits along the sutural margins can produce erosion of the suture, thereby simulating the split sutures of increased intracranial pressure [12].

Extension of paraspinal neuroblastoma into the spinal canal produces the so-called "dumbbell neuroblastoma" [6, 13]. The findings are that of a paraspinal mass that may contain calcium associated with bony erosion of the adjacent vertebral body, pedicle, or rib, and an extradural mass lesion at myelography. Long-standing intraspinal tumor will produce scalloping of the posterior aspect of the vertebral bodies and widening of the spinal canal [13].

If neuroblastoma is a diagnostic consideration, biochemical tests including urinary VMA (vanillylmandelic acid), HVA (homomandelic acid), and catecholamine levels are diagnostic if elevated. Bone marrow examination is also extremely useful, since metastases to the marrow are very common with disseminated disease.

Important radiographic examinations include films of the abdomen to search for calcification in the suprarenal and paraspinal regions. Tomography of these structures, particularly during excretory urography, or computed tomographic (CT) scanning of the abdomen [14] may be necessary for evaluation of a subtle mass. Likewise, chest films, tomograms of the posterior mediastinum, or CT scans of the chest are necessary. A radionuclide bone scan may be very helpful. Not only will occult skeletal metastases be detected, but the primary tumor may be visualized. A previous report has indicated that, in 62% of patients with neuroblastoma examined with bone scans, the primary site of neuroblastoma was visualized [15]. Angiography may be of occasional value in the preoperative histologic evaluation of the mass lesion, since neuroblastoma is a relatively vascular tumor [16].

### Presentation in the Brain and Cranium

#### Case 1: Primary Intracerebral Neuroblastoma

A 7-year-old girl had nausea and vomiting. Physical examination revealed papilledema and large scalp masses in the parietal and occipital regions. The rest of her physical examination was normal. CT demonstrated an enhancing mass in the region of the quadrigeminal plate (fig. 1A), and skull films showed lytic lesions of the calvarium (fig. 1B). Cerebral angiography demonstrated a slightly vascular mass in the posterior third ventricular region with compression of the vein of Galen and collateral venous flow around the obstructing lesion (figs. 1C and 1D). Urinary VMA values were elevated, and a radionuclide bone scan was positive in both the occiput and pineal regions. The rest of the bone scan was normal, as were a liver-spleen radionuclide scan and bone marrow aspirate and trephine. An excretory urogram showed questionable slight deviation of the left ureter, but lymphangiography, abdominal CT, and abdominal sonography were all unremarkable.

A biopsy of one of the scalp masses revealed a small-cell tumor consistent with a primitive neuroepithelial neoplasm. The patient was given whole-brain radiation therapy (3,900 rad [39 Gy]) and started on a neuroblastoma chemotherapy protocol.

She underwent exploratory laparotomy 9 months later because of the persistent and questionable left ureteral deviation, but no disease was found. She died 29 months after diagnosis, and autopsy revealed residual tumor within the pineal-quadrigeminal plate regions and within the cervical and lumbar spinal cord. There was metastatic tumor to the lumbosacral vertebrae and proximal right tibia, but no involvement of the adrenal glands, lymph nodes, or liver. By electron microscopy, the small dark cells within the cranial and spinal tumors had dendritic processes and dense core granules most consistent with a neuroblastic origin. The tumor was considered a type of "primitive neuroectodermal tumor," more specifically primary intracranial neuroblastoma.

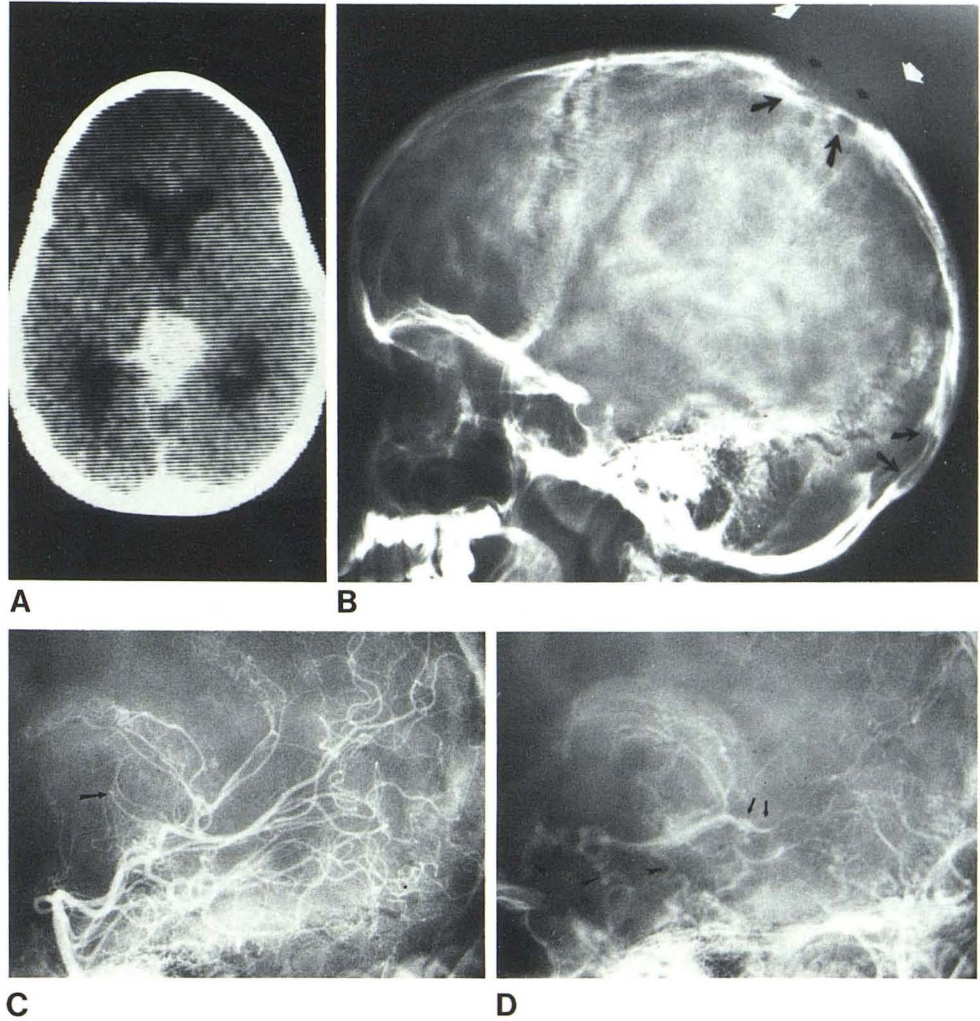
*Comments.* Primary intracerebral neuroblastoma is a recently recognized rare entity. This tumor represents one aspect of a large spectrum of primitive tumors that are best described as "primitive neuroectodermal tumors" or "embryonal gliomas" [17]. These tumors may histologically resemble extracranial neuroblastomas, with the primitive cell capable of maturation into ganglion cells and the establishment of distinctive Homer Wright rosettes in the classical form of this tumor [18]. However, identification of the neuroblastic origin of variants of this tumor, such as the transitional and desmoplastic forms [18], requires electron microscopic demonstration of dendritic processes and other histologic findings as in case 1.

In the past, these tumors were probably diagnosed as cerebral oligodendrogliomas or ependymomas. They are highly malignant and frequently metastasize to other areas of the CNS via the subarachnoid CNS pathways. In addition, they may metastasize to extraneural locations via venous invasion [19]. Therefore, the presence of scalp nodules in case 1 does not mitigate against the diagnosis of primary intracranial neuroblastoma. While an occult primary elsewhere in the body may metastasize to the scalp, metastasis of neuroblastoma to the cerebral parenchyma is an exceedingly rare phenomenon [19] and almost always occurs via direct invasion through the dura and not via hematogenous routes. Therefore, even though the patient discussed above had scalp nodules, the case is considered to be that of a primary intracranial neuroblastoma.

Primary intracerebral neuroblastoma must be considered in any child who has an apparent primary intracranial tumor. The tumor may mimic any cerebral neoplasm; however, three findings may help in differential diagnosis. The first is the relatively frequent presence of intratumoral hemorrhage [5, 20]; in one series, two of



Fig. 1.—Case 1: primary intracerebral neuroblastoma. **A**, CT scan. Large enhancing mass in region of quadrigeminal plate. **B**, Lateral skull film. Erosion of inner table of skull (*long black arrows*) in parietal and occipital regions, erosion of outer table of skull (*short black arrows*) and parietal soft-tissue mass (*white arrows*). **C**, Arterial phase of left vertebral angiogram. Anterior displacement of posteromedial choroidal artery (*arrow*) and multiple fine tumor vessels in numerous locations within mass behind third ventricle. **D**, Venous phase. Depression and compression of vein of Galen (*arrows*), with collateral venous flow (*arrowheads*).



three patients with primary intracranial neuroblastoma had large hemorrhagic components within the tumor [20]. Hemorrhage is unusual in most other childhood cerebral neoplasms. The second finding is the presence of hypervascularity on angiography [2, 16], which was present in case 1 and which will also be seen in the case of orbital metastases. Finally, calcification is relatively frequent, with one series reporting calcifications in five of 11 cases [21].

#### Case 2: Cranial Metastases

A 9-year-old Cambodian immigrant boy was in a stuporous state without lateralizing findings. He had been blind and deaf for over 1 year after an unspecified illness in Cambodia. He was generally weak, had pale optic disks, pupils that reacted sluggishly to light, and fever of 40°C. Cranial CT revealed enhancing masses in the left frontal and temporal regions, with appearances that suggested intracerebral lesions (fig. 2). Because of his rapidly worsening condition, the patient was taken to surgery, where the left frontal and temporal tumor masses were found to be totally extracerebral in position and involving the bone. The dura was displaced and thinned, but not penetrated. Postoperatively, elevated urinary HVA and VMA values were found, along with malignant cells in the bone marrow, and the diagnosis of neuroblastoma was made. A thorough search, including abdominal CT, excretory urography, chest radi-

ography, and bone scanning failed to reveal an extracranial primary site.

*Comments.* Extracranial tumor commonly metastasizes to the cranial bones and scalp during the course of the disease [9, 22], although rarely to intradural structures. In a study of 217 patients, 25% were found to have metastases to the skull and bony orbits [23]. However, an initial presentation of neuroblastoma in this manner is uncommon.

The cranial metastases of neuroblastoma are lytic in nature, with irregular margins. Scalp and epidural masses are a common accompaniment of the bony lesions [24]. The extension of tumor along the epidural margins of a cranial suture erodes bone, simulating the split sutures of increased intracranial pressure [12]. The symptoms of cranial metastases generally relate to either the pain of bony or scalp involvement, or to local pressure on the brain through the intact dura. In addition, the dural sinuses may be compressed, leading to venous stasis and increased intracranial pressure. Other major considerations of multiple cranial lytic lesions in this age group are eosinophilic granuloma, leukemia, lymphoma, and sarcomatous metastases.

There is some superficial similarity between cases 1 and 2. Primary intracranial neuroblastoma may occasionally metastasize to extradural and extraneural structures because of intracranial venous invasion. However, while blood-borne metastases from an



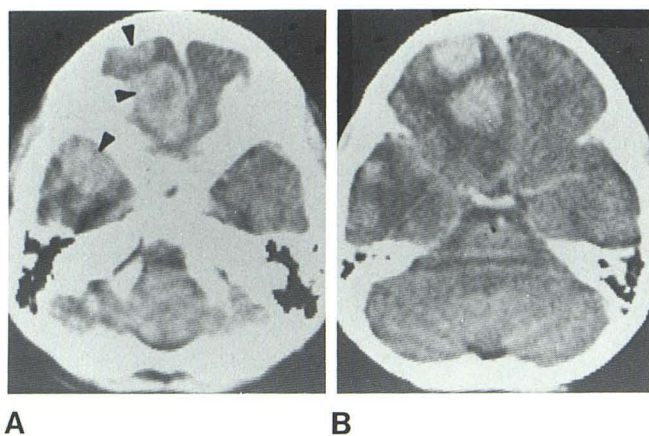


Fig. 2.—Case 2: cranial metastases. **A**, CT scan at base of skull. Three enhancing mass lesions (arrowheads) based along bony margins in left frontal and temporal regions. **B**, Slightly higher cut. Masses project into brain. Distinction between intracerebral and extracerebral masses is difficult.

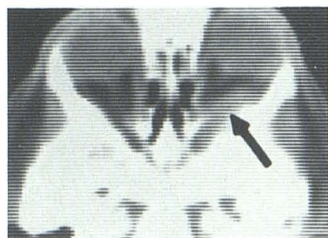


Fig. 3.—Case 3: primary orbital neuroblastoma. Unenhanced axial CT scan of orbits. Mass lesion is inseparable from right lateral rectus muscle (arrow). There was slight significant enhancement of lesion with contrast material.

abdominal or thoracic primary to the cranium and scalp are common, hematogenous metastasis to the intradural structures is exceedingly rare. The dural boundary is almost always respected even with large cranial metastases, although it may be thinned, with direct pressure placed on the brain, as in case 2, where thinning of the dura was to such a degree that, when combined with the visualization of the lesions from below, the tumor masses simulated intracerebral lesions.

## Presentation in the Orbit

### Case 3: Primary Intraorbital Neuroblastoma

A 9-month-old girl had proptosis of the right eye and a lateral rectus palsy. Orbital CT showed an elongated mass involving the lateral rectus muscle (fig. 3). The bony structures appeared intact on both CT and multidirectional tomography. The primary preoperative radiographic diagnosis was rhabdomyosarcoma of the lateral rectus muscle. A preoperative chest film was normal. Surgery revealed neuroblastoma involving the lateral rectus muscle and adjoining soft tissue and bone. Postoperatively, excretory urography, abdominal CT, bone scanning (except for the right eye), and liver scanning were normal, while bone marrow examination was positive for tumor cells. Furthermore, VMA, HVA, and urinary metanephrine levels were markedly elevated. The tumor most likely originated in the ciliary ganglion, which is located near the lateral rectus muscle.

*Comments.* The ciliary ganglion is located along the medial aspect of the lateral rectus muscle. Neuroblastoma originating in

that ganglion has been previously reported [22, 25]. Invasion of the lateral rectus muscle and the adjoining bone may follow, as in case 3. Once the tumor has invaded the bone, metastases to the bone marrow and other extraorbital sites with the production of increased catecholamine levels will occur. The differential diagnosis includes a primary tumor of the muscle such as rhabdomyosarcoma, and a distinction between these two malignant tumors on the basis of the CT alone would be impossible.

### Case 4: Orbital Metastasis

A 22-month-old boy had 1 week of progressive loss of vision preceded by 3 weeks of irritability and an upper respiratory tract infection. Skull films at another institution demonstrated destruction of the sphenoid bone. Because of fever, a diagnosis of osteomyelitis was made and intravenous antibiotics begun. Progression of the visual loss prompted transfer to the University of Minnesota, where physical examination was unremarkable except for bilateral blindness and sixth nerve palsies. Tomography confirmed destruction of the sphenoid bone (fig. 4A), and CT revealed a large mass destroying the sphenoid bone and extending into the apices of both orbits (fig. 4B). Angiography demonstrated the mass to be slightly vascular (fig. 4C). A preoperative radionuclide bone scan showed increased uptake in the sphenoid area and increased uptake in the paraspinal region of the midabdomen, which was not appreciated at the time. Emergency craniotomy and optic nerve decompression produced tissue with cells in a rosette pattern, suggesting neuroblastoma. Subsequent abdominal films revealed a calcified mass above the left kidney (fig. 4D). Catecholamines were found to be elevated, while VMA and HVA values were normal, and malignant cells were present in the bone marrow.

*Comments.* Neuroblastoma commonly metastasizes to the base of the skull and orbits late in the disease, leading to visual and oculomotor disturbances [2, 22]. However, it is unusual for neuroblastoma to present this way. In one series, only 2.8% of patients with neuroblastoma presented with visual and/or oculomotor dysfunction [25]; blindness is a very rare presentation [26]. Horner syndrome, consisting of ptosis, miosis, and anhidrosis on the affected side, may also be produced by tumor involvement of the sympathetic chain in the cervical or upper thoracic region [5, 10, 26].

Neoplasm must be the primary consideration with any destructive process of the sphenoid bone or the other periorbital facial bones of a child. Though the child in this case was febrile, bone destruction with sinusitis is rare today. A recent study of malignant facial neoplasms in children, excluding purely intraorbital tumors but including bones surrounding the orbit, including the sphenoid bone, revealed the most common tissue types as rhabdomyosarcoma, leukemia, lymphoma, and neuroblastoma [27].

## Presentation in the Spine

### Case 5: Primary Intraspinal Neuroblastoma

An 18-month-old boy had 2 weeks of progressive weakness of the lower extremities, to the point of inability to stand. He had not been toilet trained, and no changes in bowel habits could be detected by the parents. Spine films revealed deformity of the left L4 pedicle (fig. 5A), and myelography showed a large extradural mass extending from L2 to L5 (figs. 5B and 5C). Emergency decompressive surgery was performed, and a diagnosis of neuroblastoma was made. Only a few strands of tumor were found to be exiting the left L3-L4 neural foramen to lie in the paraspinal region. The amount of intraspinal tumor relative to that outside the spine



Fig. 4.—Case 4: orbital metastases. **A**, Lateral tomogram of sphenoid bone. Extensive destruction of middle and anterior parts of sphenoid bone, planum sphenoidale, and ethmoid air cells. **B**, Axial CT scan. Large mass lesion (*arrowheads*) involving sphenoid bone, and extending into orbital apices, displacing both medial rectus muscles laterally (*arrows*). **C**, Right common carotid angiogram in late arterial phase. Multiple tumor vessels (*arrowheads*) in region of body of sphenoid bone, coming from both internal and external carotid circulations. Right internal carotid artery (*curved arrow*) and chorioretinal blush of right globe (*straight arrow*). **D**, AP abdominal film. Multiple calcifications in left suprarenal region (*arrows*).

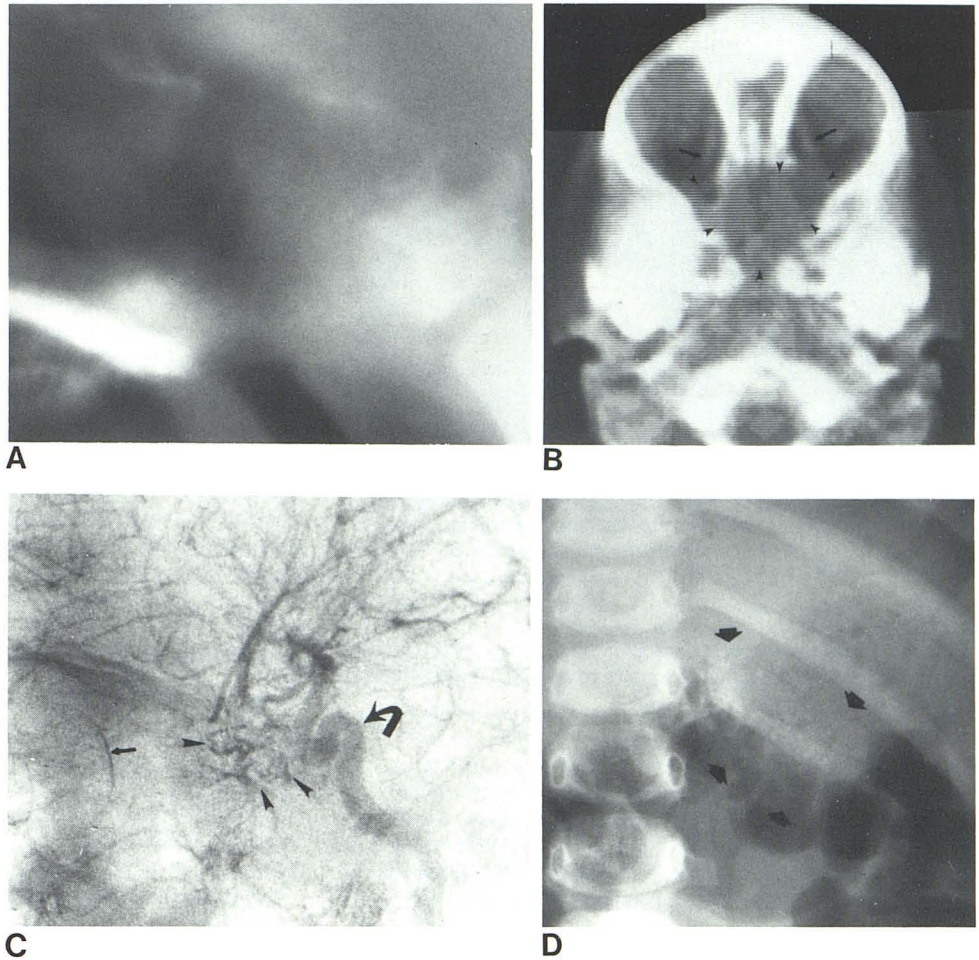
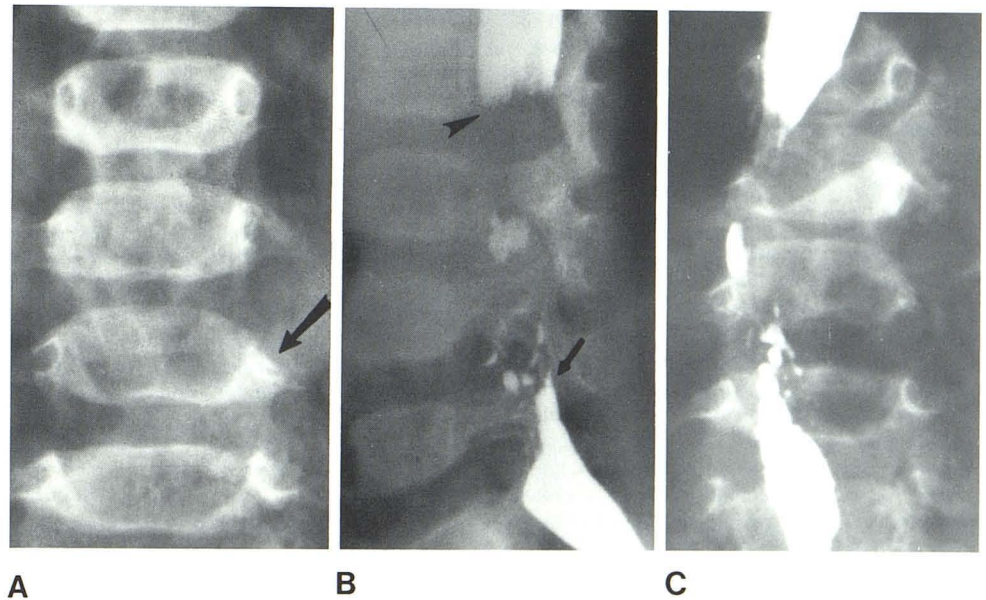


Fig. 5.—Case 5: primary intraspinal neuroblastoma. **A**, AP view of lumbar spine. Erosion of left L4 pedicle (*arrow*). Lateral (**B**) and supine (**C**) views after placement of Pantopaque into spinal canal from both lumbosacral and C1–C2 punctures. Large extradural mass on left extending from L2 to L5 and producing both cephalic (*arrowhead*) and caudal (*arrow*) extradural blocks.





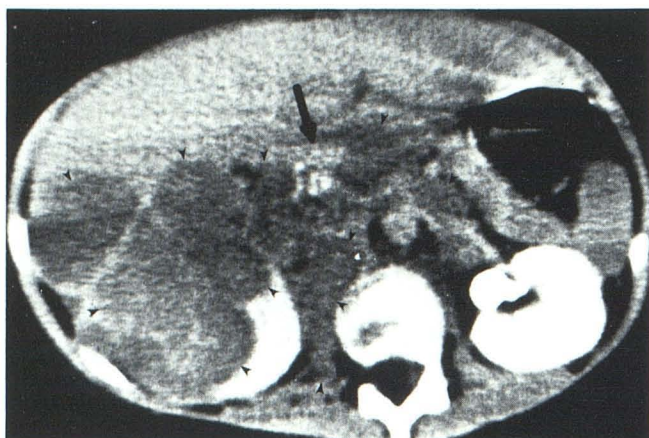


Fig. 6.—Case 6: abdominal neuroblastoma with spinal metastases. CT scan of abdomen with intravenous contrast enhancement. Large low-density tumor (*arrowheads*) within liver, right kidney, and retroperitoneal tissues. Neoplastic calcifications (*arrow*). No bony erosions present; asymmetry of neural foramina on this view is positional.

suggested primary intraspinal neuroblastoma originating in the dorsal root ganglion, which would normally lie at and just medial to the L3–L4 neural foramen.

#### Case 6: Spinal Metastases

An 11-year-old boy developed weakness of the lower extremities 3 months before admission. Of note was the patient's method of getting out of bed by backing out and pushing himself erect with his hands. Over the next few weeks, a stiff gait developed, followed by bilateral hip pain and increasingly severe abdominal pain. The patient was referred to a psychiatrist and treated with Elavil.

Physical examination on hospital admission 3 weeks later revealed a marked flaccid paraparesis, positive Babinski reflexes bilaterally, a T10 sensory level, a distended bladder, and a distended abdomen without a well defined mass. Abdominal CT revealed a large intraabdominal mass with extensive involvement of the retroperitoneum, right kidney, and liver, but without vertebral bony erosion (fig. 6). Myelography showed an extradural mass extending from T7 to T11. At a decompressive laminectomy the next day neuroblastoma was found. Postoperative VMA and HVA values were markedly elevated. The patient was placed on a neuroblastoma chemotherapy protocol.

#### Comments

Involvement of the spine by neuroblastoma is relatively common in the more advanced stages of the neoplasm. Extension of tumor through a neural foramen from a paraspinal origin produces the "dumbbell" appearance, with both an extraspinal mass that may or may not be calcified and an intraspinal extradural mass producing the myelographic findings of displacement of the entire thecal sac or a complete extradural block. Tumor may also metastasize hematogenously to a vertebral body and produce an extradural mass. While such findings are rather typical in the late course of the disease, spinal cord compression as a presenting symptom is relatively rare, occurring in only 1%–4% of cases [28].

Primary intraspinal neuroblastoma is quite rare [5, 13, 28, 29] and may occur in one of the two following ways: either primary intramedullary neuroblastoma of the spinal cord, which is exceed-

ingly rare and which is analogous to a primary intracranial neuroblastoma; or an origin from ganglion cells such as in the dorsal root ganglia. The dura extends laterally to thin out over a ganglion. Whether a neoplasm originating in this ganglion is intradural or extradural would depend on the exact site of origin and pattern of growth of the tumor relative to the dural coverings. The distinction between primary extradural but intraspinal neuroblastoma, such as in case 5, and extension of extraspinal neuroblastoma into the spinal canal may be difficult and would depend on the relative amount of tumor present in the spinal canal and that in an extraspinal location.

The differential diagnosis of an intraspinal extradural mass in childhood depends on the presence of spinal dysraphism. If dysraphism is present, the most common tumors are dermoid, teratoma, lipoma, and hemangioma, that is, tumors related to the neurocutaneous abnormality [30–32]. If there is no dysraphism, one must consider involvement by lymphoma, leukemia, neuroblastoma, and sarcomatous metastases. Thus, whether the site of metastatic involvement is the calvarium, the base of the skull and retroorbital regions, the face or the spine, the common tumors of childhood (i.e., neuroblastoma, leukemia, lymphoma, and sarcomatous metastases) must all be considered.

#### Neurological Effects from a Distant Tumor

##### Case 7: Myoclonic Encephalopathy

A 14-month-old boy had a poor appetite, broad-based gait, inability to sit without assistance, titubation of the head, myoclonic twitching of the arms, and opsoclonus ("dancing eyes" or "ocular bobbing"). Chest radiography revealed a posterior mediastinal mass. Radionuclide brain scan, bone survey, pneumoencephalogram, electroencephalogram (EEG), cerebrospinal fluid analysis, and bone marrow examination were all normal. A neuroblastoma was resected from the posterior mediastinum, and, 8 days later, the titubation and opsoclonus dramatically decreased. At the end of 3 weeks, the ataxia had greatly lessened and the patient was able to support his weight. His VMA dropped progressively throughout this time. The patient was treated with chemotherapy, and, by 6 months after surgery, he was neurologically intact, with normal VMA.

##### Case 8: Neurocristopathy

An infant presented at birth with primary pulmonary hypoventilation (Ondine curse). While no cranial nerve abnormalities were found, diffuse cerebral dysfunction was present, as evidenced by poor muscle tone, upgoing toes, abnormal reflexes on the left, and no babbling sounds. Diffuse areas of slowing were present on EEG. A metabolic workup was normal except for an elevated urinary cystine level. Cerebral angiography and pneumoencephalography were normal. The child was treated with supportive care and eventually phrenic nerve pacemakers were placed bilaterally.

At 4 months of age, chest films revealed a posterior mediastinal mass, VMA and catecholamine levels were elevated, while bone marrow examination and bone scan were normal. Surgery revealed multiple ganglioneuroblastomas involving both sympathetic chains with extension into the right adrenal gland. The multicentricity of the tumors was thought to make further therapy of little value. The child died 1 year later of respiratory complications.

#### Comments

Neurologic findings may be present without direct tumor extension into neural structures. Such is the case with myoclonic en-



cephalopathy, in which 50% of the patients have an underlying neuroblastoma, but detection of the tumor may not occur for months after the neurologic presentation [33-36]. Patients with cerebellar signs and opsoclonus should have the appropriate tests, including CT, to exclude primary cerebellar disease such as primary neoplasm. If normal, they need biochemical tests in addition to thoracic and abdominal radiography to evaluate the possibility of neuroblastoma. If such tests are negative, the tests need to be repeated weeks to months later to completely exclude underlying neuroblastoma. The mechanism for the myoclonus and opsoclonus with neuroblastoma is unclear. Various possibilities have been postulated, including metabolic factors, abnormal immune response, and/or concomitant viral infection [33-35].

The relationship of primary pulmonary hypoventilation to neuroblastoma is conjectural. This association has been reported once before, with the suggestion of a possible underlying embryologic abnormality of the neural crest tissue that gives rise to both the neuroblasts of the sympathetic nervous system and the chemoreceptor tissue responsible for the cardiopulmonary control [37]. Such an embryologic "neurocristopathy" may be responsible for fortuitous combinations of neuroblastoma with Ondine curse, and Hirschsprung disease (aganglionosis of the bowel) [37]. An abnormal neurotransmitter or transmitter metabolite, secreted by the tumor, is another intriguing possibility.

### Summary

Neuroblastoma has protean manifestations including masquerading as primary neurologic disease. The major categories of neurologic presentation have been discussed, with only esthesioneuroblastoma omitted. Esthesioneuroblastoma originates in olfactory tissue at the base of the skull and generally is seen as a nasal mass rather than with a neurologic presentation [38]. This tumor is rare in childhood.

Neuroblastoma must be a consideration in any unexplained neurologic condition in a child. While biochemical and radiologic tests may be very suggestive and/or diagnostic of the correct diagnosis, it is the realization of the possibility of neuroblastoma as the etiology of the neurologic abnormality that leads to tests and, we hope, to earlier diagnosis.

### ACKNOWLEDGMENT

We thank Joan Roberge for help in manuscript preparation.

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