Neurological involvement in the nevoid basal cell carcinoma syndrome

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Four patients who had medulloblastomas in association with the nevoid basal cell carcinoma syndrome are reported, for a total of six known cases. Involvement of the central nervous system appears to be an integral component of this syndrome. The medulloblastoma appear earlier in life (50% of the patients are less than 2 years old), and the prognosis appears to be better (five of the six are still living). Possible reasons for these features are considered, and other associated abnormalities are discussed.

KEY WORDS nevoid basal cell carcinoma medulloblastoma hydrocephalus brain tumor bone cysts

A FREQUENT component of the nevoid basal cell carcinoma syndrome is involvement of the central nervous system. Although neurological malfunctions are always included in discussions of the syndrome, a comprehensive study of these abnormalities has never been undertaken. We are presenting four new cases of the syndrome with special emphasis on its association with medulloblastoma.

In general, the nevoid basal cell carcinoma syndrome should be suspected when two or more of the following abnormalities are noted: 1) onset of multiple nevoid basal cell carcinomas early in life; 2) cysts of the jaw; 3) pitting of the palmar and plantar skin; 4) ectopic lamellar calcification of the falx cerebri; and 5) developmental anomalies of the skull, spine, ribs, and extremities. The syndrome is inherited as an autosomal dominant disorder with high penetrance and variable expressivity of the gene.

Case Reports

Case 1

A 15-month-old baby boy, the product of a full-term uncomplicated pregnancy, had been observed to have a rapidly increasing head size (48 cm) 4 months before admission. Shortly thereafter he developed unsteadiness and made no further attempt to walk without support. The fronto-occipital circumference was 55 cm (97th percentile), and the patient was lethargic. Papilledema, bilateral sixth cranial nerve palsies, bilateral extensor plantar responses, and increased deep tendon reflexes were present. Routine skull films demonstrated signs of increased intracranial pressure. A ventriculogram delineated a posterior fossa mass and moderate hydrocephalus. A grossly total removal of an intracerebellar, intraventricular medulloblastoma was carried out (Fig. 1). Postoperatively, the patient received 2500 R through
The patient received two 7-mg doses of methotrexate intrathecally on the third and fifth postoperative days. At the present time, the patient is dependent on a lumboperitoneal shunt. His parents and siblings were examined, but no evidence of the syndrome was found (Fig. 3). However, a paternal great uncle had a brain tumor classified as an astrocytoma and a remote maternal cousin had hydrocephalus.

The patient has the characteristic signs of the syndrome (Fig. 4), including frontal bossing, large head, hypertelorism, right esotrophia, and multiple bone abnormalities, including cysts of the mandible and bifid ribs. No ectopic calcifications, skin lesions, or abnormal response to parathyroid extract have been noted. He is now in his fourth year since removal of the medulloblastoma, and currently there is no evidence of recurrence.

Case 2

A 5-month-old baby boy was seen because of failure to reach normal developmental landmarks and because of a rapidly enlarging head. The diagnosis of hydrocephalus secondary to a choroid plexus papilloma was made, but no papilloma was found at the time of the operation. Subsequently, the patient had a ventriculoatrial shunt and did well until 7 years of age when he again showed signs of a posterior fossa mass. A medulloblastoma was totally removed, and radiotherapy consisting of 3500 R to the neuraxis was given over a 6-week period.
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The patient was discharged 3 months after admission with only a moderate ataxia. The patient was readmitted 2 months later because of pain in the occipital region, progressive ataxia, agitation, nausea, vomiting, and shortness of breath. She had a left myoclonic seizure and was placed on dilantin and phenobarbital. The attending physi-
died at home shortly thereafter. Recurrence of medulloblastoma in the posterior fossa as well as metastatic seeding to the lumbar subarachnoid space were found at necropsy.

Case 4

A 2-year-old boy was brought to the hospital with acute neurological symptoms and signs, the exact nature of which could not be ascertained from the available medical records. A ventriculogram revealed a markedly dilated ventricular system and a mass lesion distorting the fourth ventricle. At craniotomy, a medulloblastoma was removed. Details concerning the operative procedure and the ensuing postoperative period are not available. The patient died outside the hospital. The patient was not evaluated for the syndrome, but it was detected in his siblings, father, and numerous other relatives (Fig. 6).

Review of Associated Neurological Abnormalities

Medulloblastoma

In 1963, von Herzberg and Wiskemann first described the association between the nevoid basal cell carcinoma syndrome and medulloblastoma. They described a baby boy with a medulloblastoma plus cutaneous and osseous manifestations of the syndrome; other members of the family also had nevoid basal cell carcinomas. The medulloblastoma was surgically removed, followed by a postoperative course of irradiation. At 8 years of age the patient was well without any evidence of recurrent tumor.

In 1965, Hermans, et al., described in detail a patient who had been reported twice previously. When 4 years old, this boy had a medulloblastoma surgically removed, followed by radiotherapy treatments. Subsequently, the patient manifested multiple skin lesions, medullary fibers at the left disc margin, a dermal cyst of the maxillary sinus, and bifid ribs, and was considered to have a "very low mental endowment."

Graham, et al., in 1968 discussed a baby boy who, at 10 months, had a medulloblastoma surgically removed, followed by radiotherapy of 5000 R to the neuraxis. The patient was subsequently classified as "slow to learn." He also had hypertelorism, jaw cysts, skin lesions, and osseous abnormalities.
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In a family with the basal cell nevus syndrome, Anderson and Cook\(^1\) cited a 2-year-old boy with a medulloblastoma who died prior to examination for the syndrome. This patient is reported as our Case 4. The patient's grandfather\(^24\) was a 72-year-old man with the nevoid basal cell carcinoma syndrome, who at necropsy was found to have frontal lobe atrophy and two parenchymal cysts. Another patient with medulloblastoma, mentioned by Taylor, et al.,\(^3\) is presented in detail here as our Case 3.

Meerkotter and Shear\(^2\) in 1964 reported a 19-year-old girl with cutaneous lesions, jaw cysts, bilateral congenital cataracts, and bifid ribs. Her parents and three of five siblings were normal. One sister died at 6 weeks of age following an epileptic seizure, and a brother died at 2 years from a medulloblastoma. Gorlin, et al.,\(^1\) referred to this same patient and also mentioned a family described by Catania,\(^8\) in which one child had the syndrome and a sibling was stated to have died of a medulloblastoma. However, a review of the Catania article failed to reveal any reference to a medulloblastoma.

Other Intracranial Neoplasms

Cawson and Kerr,\(^9\) and Moynahan\(^24\) both described a patient with multiple nevoid basal cell carcinomas, ophthalmological abnormalities, mental retardation, and a cerebellar astrocytoma which was successfully removed surgically. Kahn and Gordon\(^19\) presented a patient who died at the age of 16 days and was found to have multiple periventricular nodules composed of astrocytic cells (a histological picture similar to tuberous sclerosis, but without giant or abnormal astrocytes) as well as basal cell nevi, bilateral corneal opacities, leiomyomas of the bowel, and cysts of the choroid plexus in the third and lateral ventricles. Telle\(^3\) reported siblings with the nevoid basal cell carcinoma syndrome in which one member had a posterior fossa meningioma. A 64-year-old man with manifestations of the nevoid basal cell carcinoma syndrome was found at necropsy to have both a craniopharyngioma and a meningioma.\(^33\) Another sibship was described by Kennedy and Abbott\(^30\) in which a 2-year-old girl died of a brain stem tumor. The histological diagnosis was not available, and she did not have any evidence of the syndrome.

Also, the central nervous system or the eye may be involved with secondary tumor formation by malignant transformation of the nevoid basal cell carcinoma with either direct extension or metastatic deposits.\(^34\)

**Congenital Abnormalities of the Central Nervous System**

Partial agenesis of the corpus callosum is usually the first neurological abnormality which comes to the clinician's mind when
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this syndrome is encountered, because of the original description by Binkley and Johnson. Their patient had no clinical manifestations of neurological abnormalities, but at necropsy a partial agenesis of the corpus callosum was found. Subsequently, no additional patients with any abnormality of the corpus callosum have been described.

Clendenning, et al., stated that there may be associated absence of the gyrus fornicatus and falx, and fusion of the frontal hemispheres.

Hydrocephalus

Hydrocephalus is frequently mentioned as a primary neurological manifestation of the nevoid basal cell carcinoma syndrome. Yet, to date, only two patients have been reported with hydrocephalus that was primary, not secondary, to a neoplasm. The other patients have had neoplasms as the cause of their hydrocephalus.

Ophthalmological Abnormalities

The nevoid basal cell carcinoma syndrome has been termed the "fifth phakomatosis." Abnormal findings include hypertelorism, enophthalmic appearance (resulting from frontal bossing or overdevelopment of the supraorbital ridges), strabismus, congenital corneal opacities, cataracts, microphthalmia, congenital blindness, chalazia, and nevoid basal cell carcinomas on the upper lid which may invade the intraorbital contents.

Emotional and Intellectual Disturbances

In their original description, Binkley and Johnson stated their patient was "mentally dull." Since that time, various intellectual and emotional aberrations have been mentioned, but few have been thoroughly evaluated.

X-ray Abnormalities Related to the Central Nervous System

Roentgenographic abnormalities have been discussed extensively in other articles on this subject. Abnormalities of the spine include scoliosis, kyphoscoliosis, spina bifida occulta, fusion of the spinous processes, narrowed intervertebral spaces, and degenerative changes of the vertebral bodies.

Findings on routine skull films include a shallow sella turcica, bridging of the sella turcica, frontal and/or parietal bossing, overdevelopment of the supraorbital ridges, asymmetry of the skull, broad nasal root, platybasia, prognathism, and cysts of the maxilla and mandible.

Ectopic intracranial calcifications have received considerable attention. Sixty-seven percent of involved patients have lamellar calcification of the falx, and the average age at appearance is 22 years. Calcification has also been described in the tentorium, petroclinoid ligament, dura, pia, choroid plexus, and basal ganglia. Calcification in each of these sites has been well documented, except for the basal ganglia, which has yet to be demonstrated. Should this exist, both seizures and mental retardation could be accounted for on the basis of basal ganglia involvement. The usual extrapyramidal findings have not been noted in these cases. To date, there is no known case of involvement of the basal ganglia. The presence of calcification in this location appears unlikely, but if subsequent studies should demonstrate its presence, then a different mode of calcium deposition would have to be considered.

Miscellaneous Abnormalities

Cortical atrophy, intracerebral cystic areas, disturbance of micturition due to falx calcification, and seizures are other findings reported in some few patients. Swift and Horowitz described a large family with Charcot-Marie-Tooth disease and several of its members had the nevoid basal cell carcinoma syndrome.

Discussion

Discussions of the nevoid basal cell carcinoma syndrome generally refer to the occasional presence of medulloblastoma. In fact, it first appeared that nine such cases were recorded in the literature, but careful review verified only three. In this work we are adding three new cases.

A patient may have a medulloblastoma and be a member of a kinship which manifests the nevoid basal cell carcinoma syndrome, but may not be known to have the syndrome himself. Meerkotter and Shear reported such a case and our Case 4 fits into this category. Both of these patients died at
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2 years of age and had not been investigated for the syndrome.

Various aspects of these medulloblastomas should be considered. The histopathological characteristics are the same as those of other medulloblastomas, but the apparent course of the disease is unusual. Of the six known cases, five are living and doing well without evidence of recurrence 2, 5, 7, 8, and 9 years after surgery, and the other one died of recurrent medulloblastoma at 5 years of age, 1 year after surgical removal and irradiation.

The average survival in most large series of sporadic medulloblastoma, however, is 3 years following surgery alone; if irradiation is added, a 5-year survival rate for 62% of the patients has been recorded and a 7-year survival rate for 23%. The inclusion of chemotherapy may provide an even longer survival time.

Several explanations seem apparent. Medulloblastomas associated with the nevoid basal cell carcinoma syndrome may be basically different, but currently there is no evidence to substantiate this notion. Or it may be that too few members of these families have been fully evaluated and followed, so that all that is known about certain persons is that they died of "hydrocephalus," "seizures," or "brain tumor;" some may have harbored unrecognized medulloblastomas. The patient known to have the syndrome in association with a medulloblastoma may be one whose tumor was less virulent, and who therefore lived far longer than would generally be expected. Another consideration is that patients who died at a very early age might have demonstrated manifestations of the syndrome if they had lived longer or had been specifically evaluated for the syndrome.

Another interesting finding in these patients with medulloblastoma is that they have presented central nervous system signs and symptoms at a surprisingly early age. Of these six patients, one was 5 years old, two were 4 years old, one was 15 months old, one was 10 months old and one was an infant, for an average of almost 2.89 years. In the general population of medulloblastomas, symptoms usually appear within the first 10 years, and most patients range in age from 6 to 10 years. When considering the pediatric population alone, the mean age is as young as 5.5 years. It is unusual to find medulloblastomas in children less than 2 years old.

Five of the six cases were in males (83%). This ratio is slightly higher than that in most series of medulloblastoma. In other series, 57% to 75% are male. Our only girl was also the only Negro, and it is stated that the appearance of nevoid basal cell carcinomas in the Negro race is quite rare. This young patient had most of the manifestations of the nevoid basal cell carcinoma syndrome, but did not have the carcinomas.

The associated abnormalities are not as common as was previously believed. Occasionally, astrocytomas or meningiomas may be present. Congenital anomalies and seizures are rare. Hydrocephalus, when present, is usually secondary to a mass lesion. These patients are frequently labeled as being mentally retarded, but complete psychological and psychiatric evaluations have seldom been performed.

**Summary**

Involvement of the central nervous system is an integral part of the nevoid basal cell carcinoma syndrome. Congenital anomalies, hydrocephalus, seizures, ophthalmologic abnormalities, mental and emotional disturbances, medulloblastomas, and other types of brain tumors all have been related to this syndrome. The associated medulloblastomas that do occur have some basic features that are unusual, particularly their early onset and longer survival rate. Medulloblastomas also have been described in patients with a family history for the syndrome, but who, at the time of death, did not manifest the syndrome. Four new cases have been presented.

**References**

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