Familial Pheochromocytoma with Ependymoma of the Spinal Cord

Case Report and Review of the Literature*

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Multiple neurofibromatosis occurs in 5–25 per cent of patients with pheochromocytomas.1,3,4 The first recorded case of pheochromocytoma with a meningioma of the foramen magnum without evidence of neurofibromatosis was reported by Greenhouse in 1961.1 He felt that this was more than a fortuitous relationship, since meningiomas are a frequent accompaniment of neurofibromatosis. His review of the literature emphasized the relationship of pheochromocytoma to the other manifestations of multiple neurofibromatosis. He felt that his case might provide further evidence to justify the concept that the neurocutaneous syndromes—multiple neurofibromatosis (von Recklinghausen’s disease), tuberous sclerosis (Bourneville’s disease), meningo-facial angiomatosis (Sturge-Weber’s disease) and cerebello-retinal hemangioblastomatosis (von Hippel-Lindau’s disease)—are connected with pheochromocytomas. If so, one would expect tumors of other neural elements to occur in combination with pheochromocytomas as they do with the other neurocutaneous syndromes.

Recently, a girl with familial pheochromocytoma and an associated ependymoma of the spinal cord was studied on the neurologic service of the Los Angeles County General Hospital. This patient showed no evidence of multiple neurofibromatosis despite the notable association of ependymomas with multiple neurofibromatosis.2 We are presenting her case and shall discuss its possible significance.

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Report of Case

The patient’s brother was the first to present himself to the Los Angeles County General Hospital. Prior to his admission he had recurrent episodes of excessive sweating since the age of 15. On occasion these were so severe that he had cramps in his muscles and encrustations of salt in his shirt. In January 1960, at the age of 20, he was admitted in shock with severe dehydration following an attempted 8-day drive through the desert. He responded to appropriate symptomatic therapy and was found to have markedly elevated urinary catecholamines. Surgical explorations revealed a left adrenal pheochromocytoma, a right adrenal pheochromocytoma, a left ectopic pheochromocytoma and a right ectopic pheochromocytoma. These were all removed. Dr. Shannon Brunjes screened 14 members of the boy’s family in three generations for urinary catecholamines. Significantly elevated levels were demonstrated in the boy’s father and in one sister of a sibship of four. This sister, our patient, is a 13-year-old white female.

She was admitted to the Los Angeles County General Hospital in March 1961 for further studies. Her only complaint at that time was intermittent sweating, flushing and swelling of her hands and to a lesser degree her feet. An elevated blood pressure had never been demonstrated.

Examination and numerous laboratory tests, including intravenous urograms and retroperitoneal pneumography, revealed no abnormalities.

Operation. An exploratory laparotomy in April 1961 revealed a pheochromocytoma on the right adrenal gland which was removed by a partial adrenalectomy. The left adrenal gland was visualized as normal and no ectopic tumors were noted.

Histologic Report (Dr. Weldon Bullock). Sections of this tumor were typical of pheochromocytoma (Fig. 1).

Course. The patient complained of severe pain in the right side of her neck on the 4th postoperative day. This complaint may have been present in a mild form prior to operation. Roentgenograms of the cervical spine, right scapula and shoulder were taken and reported as being within
normal limits. Her postoperative urinary catecholamines were normal.

During visits to the clinic the patient was noted to have flushing and moisture of her hands and complaints of ever worsening pain in the neck. This pain became progressively worse despite temporary relief from physical therapy. She was unable to sleep, except in a near-sitting position, by September 1961. Whenever the pain in the neck was severe, standing and walking would relieve it to some degree. She became aware of weakness in both arms, more marked on the left, during the few months prior to her second admission to the neurologic service in November 1961. Coincident with this was an increased tendency to drop objects. She became so disabled prior to admission that she was unable to successfully button and unbutton her clothes or dress herself.

Examination on 2nd admission revealed an alert, cooperative, thin and anxious young girl. There was obvious atrophy of the muscles in the left upper extremity proximally and in the shoulder. She had moist, mottled, bluish discoloration of both hands with minimal puffiness. Blood pressure was 120/80, and pulse was regular, with a rate of 100. Her face had an erythematous hue over both malar areas. The feet were cold and slightly erythematous.

Neurologic examination revealed a thin girl with markedly reduced masses of muscles generally. She held her neck very rigidly in an extended position. She was unable to tolerate movement of the neck in any direction. There was marked suboccipital tenderness to palpation bilaterally. She evidenced obvious atrophy of the muscles of the shoulder bilaterally, most marked on the left. She was weak in all the muscles tested in both upper extremities. The weakness was most marked in the proximal left arm. She was unable to abduct the arm or flex the elbow against gravity. An early flexor contracture of the middle finger of the left hand was seen. The triceps reflex was absent in the left upper extremity and hyperactive in the right upper extremity. The finger reflexes were not active in the fingers but a marked reflexogenous spread could be seen in the muscles of the shoulder bilaterally. Percussion of the groups of muscles over the shoulders showed increased irritability. The deep tendon reflexes were hyperactive in both lower extremities. Plantar stimulation of the right foot produced a questionable extensor response. Response on the left was flexor. The patient evidenced marked stereanesthesia in the left hand with only slight loss to sensation of a pin in the fingertips of both hands. Sense of position was absent in the left arm, hand and ankle. There was mild cerebellar dysmetria in both hands. The cranial nerves were normal including the fundus. Her radial pulses were readily obliterated with abduction of the shoulders. Roentgenograms of the skull were unremarkable. Roentgenograms of the cervical spine revealed a questionable change when compared to those taken at the onset of her difficulty 7 months previously. This consisted of

Fig. 1. Right adrenal pheochromocytoma.
mild scalloping of the posterior border of the vertebral bodies as seen on lateral views. There was an apparent increase in the anteroposterior diameter of the canal. This was evident, in retrospect, in the cervical roentgenograms of 7 months before.

Electromyograms revealed no potentials of spontaneous fibrillation. Complex polyphasic motor units were observed in almost all muscles in the upper extremities. The right biceps, first dorsal interosseus and opponens pollicis revealed positive sharp waves.

Subsequent examinations revealed questionable sensory hyperalgesia to pin from the mid-chest to the neck bilaterally and a fluctuating ptosis and miosis in the left eye.

Cervical myelography performed on the 2nd hospital day revealed extensive widening of the cord extending from the level of C2 to T11, but most marked in the cervical region.

2nd Operation. A cervical thoracic laminectomy was performed by Dr. Theodore Kurze. On opening the dura mater a large tortuous, dilated vessel was seen with a serpentine configuration extending from C4 to C7, under the arachnoid, involving the surfaces of the left dorsal quadrant of the cord. The cord was two or three times its normal size in transverse and anteroposterior diameter with flattening and stretching of the posterior cervical roots. Through an incision to the left of the posterior longitudinal sulcus a pinkish-gray tumor was seen and biopsied. It was technically impossible to proceed beyond biopsy at that time because of an obstruction to the airway.

Histologic Report. Sections of this tumor were consistent with ependymoma (Fig. 2).

Course. She had an essentially uneventful postoperative course with subsidence of the pain in the neck. Following discharge the patient received radiation therapy to the cervical and upper thoracic spine. Postoperative urinary catecholamines remained within normal limits.

Follow-up examination in October 1962 revealed minimal complaints of the neck except for stiffness and tiredness with some aching when the head was unsupported for protracted periods. She sleeps horizontally in good comfort. She is making good gains in daily activities and has returned to a moderately active life and to school this fall. There is fair strength of the proximal muscles of her arm and moderate strength in her distal muscles. No fasciculations can be seen. She can button and unbutton her clothes with more skill. She maintains an increasingly marked lumbar and cervical lordosis. The deep tendon reflexes are reduced in the upper extremities generally. The leg reflexes remain hyperactive with no pathological toe signs. Sense of vibration is lost in the distal arms and legs bilaterally. Sense of position is absent in the fingers bilaterally. There is a slight hyperalgesia in a glove distribution over both hands. She has shown no ptosis or miosis in the left eye. The discoloration and moistness of the hands is minimal to absent.

Fig. 2. Ependymoma from biopsy of cervical cord.
Discussion

Prior to laminectomy this patient was felt to have a neurofibroma or meningioma of the foramen magnum related to the pheochromocytoma. The demonstration of an ependymoma of the spinal cord suggested either a coincidence of two rare conditions or, more likely, another example of pheochromocytoma as a familial dysgenetic disease.

The remarkable incidence of neurofibromatosis in patients with pheochromocytoma is well documented and accepted.

Glushien et al. described 2 cases of angiomatosis retinae associated with pheochromocytoma and cited a case of Wolf and Wilens with multiple hemangioblastomas of the spinal cord, cystic cerebellar hemangioblastoma, syringomyelia, congenital cysts of kidneys and pancreas and a benign hypernephroma associated with pheochromocytoma. They suggested that pheochromocytoma is related not only to multiple neurofibromatosis but also to cerebroretinal hemangioblastomatosis and possibly the other neurocutaneous syndromes. Later, Chapman et al. reported a patient with pheochromocytoma, neurofibromatosis and a cerebellar hemangioma and also a patient with pheochromocytoma, multiple brainstem hemangiomas and a family history of both cerebroretinal hemangioblastomatosis and multiple neurofibromatosis. Meredith and Hennigar reported a case of cystic cerebellar hemangioma with neurofibromatosis and pheochromocytoma. Pyzik reported intraspinal angioma and retinal angiomaticosis in a patient with a pheochromocytoma. Pheochromocytomas therefore appear definitely to be related to two of the neurocutaneous syndromes. They have been documented as being variously associated with thyroid carcinoma and parathyroid adenoma on a familial basis, renal carcinoma, ovarian carcinoma, ovarian cystadenoma and metastasizing schwannoma of the mediastinum.

Although the so-called neurocutaneous syndromes seem difficult to characterize as a group, they have certain unique features. There exists with each a central core of pathology embodied in characteristic multiple lesions. Associated with each is a variable fringe of other neoplastic, hamartomatous or congenital lesions. These conditions are heredofamilial and seemingly congenital and can occur in fragmentary form. Another characteristic of this group is the overlap between them, seen in individual patients. Neurofibromas and café-au-lait spots occur in cerebroretinal hemangioblastomatosis and tuberous sclerosis. Retinal angiomias are seen in tuberous sclerosis and neurofibromatosis. Retinal and optic-disc tumors have been found in tuberous sclerosis and neurofibromatosis.

Assuming a central core of pathology in the adrenal and ectopic pheochromocytoma with occasional ganglioblastic and neuroblastic changes, we might conclude that Greenhouse's foramen-magnus meningioma and our spinal-cord ependymoma, present in the absence of any other neurocutaneous syndrome, represent evidence for the associated, variable fringe of hamartomatous or neoplastic lesions. Evidence is clear for overlap with other neurocutaneous syndromes, neurofibromatosis and cerebroretinal hemangioblastomatosis. The criteria left to be satisfied are those of multiplicity of the lesions and a heredofamilial condition.

Recently pheochromocytomas have been shown to be impressively familial and multiple. With the addition of his own cases, Cushman reviewed 32 cases of pheochromocytoma in 12 kindred. He noted that this familial variety of pheochromocytoma tends to occur at a younger age, has a greater incidence of multiplicity and is transmitted as an autosomal dominant with good penetrance. This is demonstrated in our patient. Her brother had multiple pheochromocytomas. In a sibship of 2 males and 2 females one of each sex had the disease, suggesting good penetrance of an autosomal dominant. The onset was at a young age. Interestingly, Cushman felt that all pheochromocytomas
may be genetically determined since the incidence of familial to sporadic cases reported in the literature is 33:380.

The remarkable report of Tishelman et al. was published recently and provides impressive support for this concept. They examined 199 members of a kindred containing approximately 500 persons in five generations. Of these 199 members, 7 had proven pheochromocytomas, 22 members had café-au-lait spots 1.5 cm. in diameter or greater, 2 had extensive cutaneous hemangiomas and 2 others had angiomatosis retinae. The other miscellaneous, associated anomalies in this kindred are impressive.

Summary

A case of familial pheochromocytoma associated with an ependymoma of the spinal cord is presented because it seems to more strongly suggest that there may be a pheochromocytoma complex as another member of the so-called neurocutaneous syndromes. This case also suggests the need to look for pheochromocytomas in all neurocutaneous syndromes, especially if there is hypertension, and to look for neurocutaneous stigmata and familial occurrence in cases of pheochromocytoma.

References


