Hypertension and Neurofibromatosis
Case Report

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SUMMARY A 14-year-old girl with neurofibromatosis presented with severe hypertension. She was subsequently found to have a cerebellar glioblastoma multiforme and vascular lesions producing coarctation of the abdominal aorta and 50% and 95% stenosis of the left and right renal arteries respectively. No evidence of pheochromocytoma was found. After removal of the cerebellar tumor, marked amelioration of the hypertension suggested that the tumor had a major role in the pronounced elevation of her blood pressure. Patients who have both neurofibromatosis and hypertension should be carefully evaluated for these several potential lesions. (Hypertension 4: 894–897, 1982)

KEY WORDS • neurofibromatosis • cerebellar tumor

eurofibromatosis is a hereditary disorder that may affect any organ system. The characteristic tapered, stenotic vascular lesions associated with this disease were first recognized in the 1940s by Reubi1 and Feyrter.2 When these lesions affect the abdominal aorta or the renal arteries, arterial hypertension may develop, and at least 48 such cases have been described.3 Neurofibromatosis is also associated with an increased incidence of neoplasia, notably intracranial tumors1 and pheochromocytomas.5 As either of these may also produce hypertension, the patient with both neurofibromatosis and hypertension may have several potential secondary causes for the elevated blood pressure. We recently treated a 14-year-old girl with severe hypertension and neurofibromatosis in whom vascular lesions produced both abdominal aortic coarctation and renal artery stenosis. She also had a cerebellar glioblastoma near the fourth ventricle, which proved ultimately to be a major factor in her pronounced blood pressure elevations.

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Received December 22, 1981; revision accepted June 16, 1982.

Case Report

A 14-year-old white girl from a family without a history of neurofibromatosis was evaluated in September 1980 for phobic behavior, unsteady gait, and lethargy. Pulse was 80 beats/min and blood pressure was 168/130 mm Hg in her right arm (sitting), 170/120 mm Hg in her left arm, and 120/90 mm Hg in her left leg. Bilateral papilledema and marked arteriolar constriction with two flame hemorrhages were seen during funduscopic examination. Pansystolic bruits were heard in the left parasternal and interscapular areas as well as in the epigastrium, which radiated to both flanks. Weak femoral arterial pulses were present. On her thorax she had at least 11 café au lait spots ranging from 1 to 4 cm in diameter, and had bilateral axillary freckling. No cutaneous fibromas were observed. She was alert and oriented, with a mild left facial nerve weakness of the central type. Nystagmus on left horizontal gaze was noted. Gross ataxia in all extremities was present together with a wide-based unsteady gait and bilateral extensor plantar reflexes.

Complete blood count, serum electrolytes, urea nitrogen, glucose, calcium, uric acid, and creatinine were all normal. A chest x-ray showed normal cardiac size and notching of inferior rib margins. An electrocardiogram revealed T-wave inversion in leads 1, aVL, and V1–V4. A computed tomographic scan of her head displayed enlargement of the third and lateral ventricles together with a lesion 3.7 cm in diameter
near the cerebellar vermis filling the fourth ventricle, which was enhanced by intravenous contrast material (fig. 1). Twenty-four-hour urinary vanillylmandelic acid (VMA) excretion was 5.9 mg (normal < 7), metanephrines 0.7 mg (normal < 1.0), epinephrine 13.1 μg (normal < 20), and norepinephrine 56.1 μg (normal < 80). Supine plasma norepinephrine concentration was 238 pg/ml (normal < 400), and epinephrine was 43 pg/ml (normal < 80). Plasma renin activity was 2.8 ng/ml/hr (normal < 2.5).

The hypertension was treated with oral propranolol and prazosin in total daily doses of 320 and 9 mg a day respectively, producing control of her blood pressure after 5 days, to 140/90 mm Hg or below. A ventriculoperitoneal shunt was then inserted to relieve increased intracranial pressure (measured as > 50 cm H₂O) produced by her noncommunicating hydrocephalus.

When a pheochromocytoma was excluded by the finding of normal levels of catecholamines and metabolites, bilateral renal and abdominal aortic angiography was performed. This showed coarctation of the abdominal aorta from the suprarenal level of the aorta to the level of the third lumbar vertebra. Incorporated within this coarctation was a 50% stenosis of the left renal artery and a 95% stenosis of the right, the latter lesion associated with poststenotic aneurysmal dilatation (fig. 2). Additional findings were stenosis of the superior mesenteric artery and a dilated arc of Riolan (a large branch of the middle colic artery in the transverse mesocolon), which provided collateral flow to the inferior mesenteric artery and aortic bifurcation.

Cerebral arteriography confirmed an avascular mass in the region of the inferior vermis quadrigeminal cistern. Posterior fossa craniotomy was performed, and a soft, gray, friable tumor filling the fourth ventricle was removed from beneath the vermis. Pathologic examination showed a highly cellular, pleomorphic glioblastoma multiforme with abundant multinucleated giant cells (fig. 3).

Blood pressure control, both intraoperatively and postoperatively, was achieved with intravenous nitroprusside. This drug was discontinued by the third postoperative day when her blood pressure remained stable at 150/100 mm Hg. She was subsequently treated with superfractionated radiation to the posterior fossa of 1000 rads weekly for 7 weeks. Persistent blood pressure elevations of approximately 150/100 mm Hg during the subsequent weeks prompted reinstitution of antihypertensive therapy with propranolol (160 mg daily) together with hydrochlorothiazide (50 mg daily); blood pressure was reduced to 120/80 mm Hg. No tumor recurrence was evident on follow-up at 6 months.

**Discussion**

Neurofibromatosis (von Recklinghausen's disease) results from dysplasia of many tissues, primarily those of the neuroectoderm and to some extent mesoderm. Clinical signs include café au lait spots, multiple soft cutaneous tumors, and palpable neurofibromas of pe-

**FIGURE 1.** Contrast-enhanced computed tomographic scan of the brain demonstrates a midline-enhancing mass in the quadrigeminal cistern with obstructive hydrocephalus of the third and lateral ventricles.

**FIGURE 2.** Subtraction film of an abdominal angiogram reveals bilateral renal artery stenosis (arrows) and coarctation of the abdominal aorta. The arterial catheter fills the lumen of the narrowed distal aorta.
micrograph showing a moderately pleomorphic, astrocytic neoplasm with numerous multinucleated giant cells, numerous mitotic figures, small foci of necrosis, and endothelial proliferation characteristic of glioblastoma multiforme (× 960).

At least two types of arterial abnormalities may be present in neurofibromatosis. One type affects predominantly smaller vessels and involves concentric intimal proliferation and thinning of the media. A related lesion affects larger vessels and includes marked intimal fibrous thickening, irregular smooth muscle loss, fragmentation of elastic tissue within the media, and occasionally proliferation of epithelioid cells forming nodules. Bilateral renal artery stenosis and abdominal aortic coarctation are often associated. The characteristic radiologic appearance is of smoothly-bordered stenotic segments continuing into elongated funnel-shaped channels, found most often in children or young adults. These lesions differ from those of fibromuscular dysplasia both by their appearance and by their location. Most renal arterial stenoses are proximal in neurofibromatosis, whereas 95% of fibromuscular lesions are within the distal segment of the renal artery. The renal artery stenosis of one patient with vascular neurofibromatosis has been successfully dilated using percutaneous transluminal angioplasty. Although renovascular hypertension has not yet been established as a diagnosis for our patient, the high grade stenosis of her right renal artery and mildly elevated plasma renin activity favor this diagnosis.

Intracranial tumors occur with increased frequency in neurofibromatosis and are most often acoustic neuromas, meningiomas, and gliomas. Six malignant tumors classified as glioblastoma multiforme of the cerebellum have been reported in patients with neurofibromatosis, and only nine glioblastomas of the cerebellum have been reported in children (both with and without neurofibromatosis). In our patient, the unusual feature of the cerebellar glioblastoma was its apparent contribution to her markedly elevated blood pressure. Tumors in the posterior fossa may produce severe hypertension, occasionally paroxysmal in type and mimicking pheochromocytoma. Hypertension results from compression and subsequent stimulation.

Peripheral nerves. All or none of these lesions may be present in a given affected individual. Our patient had classic café au lait spots. Her predominant lesions, however, were those causing her extensive arterial disease, which is common in neurofibromatosis. Vessels of any organ may be affected, with lesions of the renal arteries being most frequently reported. At least two types of arterial abnormalities may be present in neurofibromatosis. One type affects predominantly smaller vessels and involves concentric intimal proliferation and thinning of the media. A related lesion affects larger vessels and includes marked intimal fibrous thickening, irregular smooth muscle loss, fragmentation of elastic tissue within the media, and occasionally proliferation of epithelioid cells forming nodules. Bilateral renal artery stenosis and abdominal aortic coarctation are often associated. The characteristic radiologic appearance is of smoothly-bordered stenotic segments continuing into elongated funnel-shaped channels, found most often in children or young adults. These lesions differ from those of fibromuscular dysplasia both by their appearance and by their location. Most renal arterial stenoses are proximal in neurofibromatosis, whereas 95% of fibromuscular lesions are within the distal segment of the renal artery. The renal artery stenosis of one patient with vascular neurofibromatosis has been successfully dilated using percutaneous transluminal angioplasty. Although renovascular hypertension has not yet been established as a diagnosis for our patient, the high grade stenosis of her right renal artery and mildly elevated plasma renin activity favor this diagnosis.

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of vasomotor centers located within the posterior hypothalamus and in regions neighboring the fourth ventricle. The tumor in our patient impinged upon these areas, and the marked amelioration of her hypertension following tumor removal suggests that this lesion produced a major component of her hypertension. Unlike previously described cases, however, her hypertension was not paroxysmal but was sustained, and she had no other symptoms of excessive sympathetic activation. Although about 5% of pheochromocytomas are associated with neurofibromatosis, our patient had no evidence for this tumor. In fact, the association of pheochromocytoma with neurofibromatosis is very rare in children.

Our patient illustrates the actual and potential causes of secondary hypertension in patients with neurofibromatosis. She did not have a detectable pheochromocytoma, but did have vascular lesions and a cranial neoplasm, both of which were contributory factors to her severe hypertension. Patients with both neurofibromatosis and hypertension should be scrutinized for all of these potential lesions.

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Hypertension. 1982;4:894-897
doi: 10.1161/01.HYP.4.6.894

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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