Case Reports

Revascularization in a 17-Year-Old Girl with Neurofibromatosis

and Severe Hypertension Caused by Renal Artery Stenosis

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Renal artery stenosis caused by neurofibromatosis is a rare cause of renovascular hypertension. This hypertension can develop during childhood and is one of the leading causes of poor outcome.

We report the case of a 17-year-old girl who was incidentally diagnosed with severe hypertension. During her examination for secondary hypertension, we reached a diagnosis of neurofibromatosis type 1 on the basis of a cluster of typical findings: optic nerve glioma, café au lait spots, nodular neurofibromas, and axillary freckling.

Renal angiograms revealed a hemodynamically significant left renal artery stenosis (70%). Renal angioplasty with a self-expanding stent was performed one month later for rapidly progressive renal artery stenosis (90%) and uncontrolled blood pressure. Excellent blood pressure control resulted immediately and was maintained as of the 2-year follow-up evaluation. We think that percutaneous transluminal renal angioplasty can be effective in select patients who have neurofibromatosis type 1 and refractory hypertension caused by renal artery stenosis. ***(Tex Heart Inst J 2017;44(1):50-4)***

Key words: *Blood pressure monitoring, ambulatory/methods; hypertension, renovascular/diagnosis/etiology/radiography/therapy; neurofibromatosis 1/complications/metabolism/pathology; renal artery obstruction/complications/pathology/therapy; treatment outcome; vascular diseases/physiopathology*

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Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder. It is caused by mutations in the *NF1* gene that lead to the production of a nonfunctional version of neurofibromin that cannot regulate cell growth and division.[1] This rare condition is frequently associated with hypertension, mostly secondary to renal artery (RA) stenosis in younger patients.[2] Vascular abnormalities such as stenoses and aneurysms are a main cause of death in NF1 patients.[3] Associated RA stenosis can increase the mortality rate because of the greater risk of cardiovascular events. We present the case of a teenager with NF1 and discuss our treatment decisions.

Case Report

In November 2014, a 17-year-old girl was referred to our cardiology department for asymptomatic severe hypertension—blood pressure (BP) as high as 240/120 mmHg—incidentally diagnosed 6 weeks earlier. The patient was screened for secondary causes of hypertension. The patient's family history was negative for hypertension and neurofibromatosis.

Clinical evaluation revealed a short teenager (height, 150 cm; weight, 58.5 kg) with abdominal obesity. Pigmented skin lesions characteristic of NF1 were noted (Fig. 1). The patient's BP at presentation was 175/110 mmHg in both arms (heart rate, 98 beats/min). Her peripheral pulses were normal, and there were no detectable heart, abdominal, or vascular murmurs.

An electrocardiogram showed sinus rhythm and left ventricular hypertrophy (Sokolow-Lyon index, 43 mm). A chest radiograph showed nothing unusual. Laboratory findings included mild anemia (hemoglobin, 11 g/dL) and elevated levels of plasma renin (264 pg/mL) and aldosterone (599 ng/dL). Renal and liver func-

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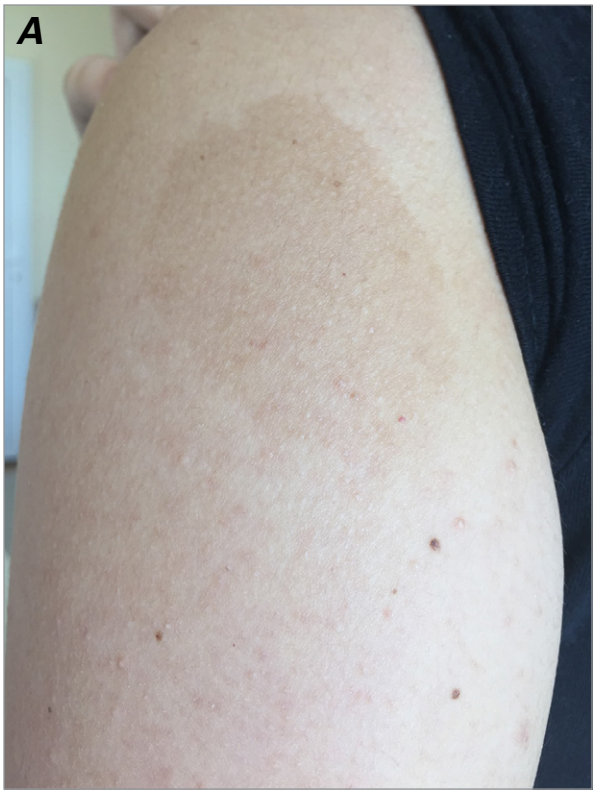

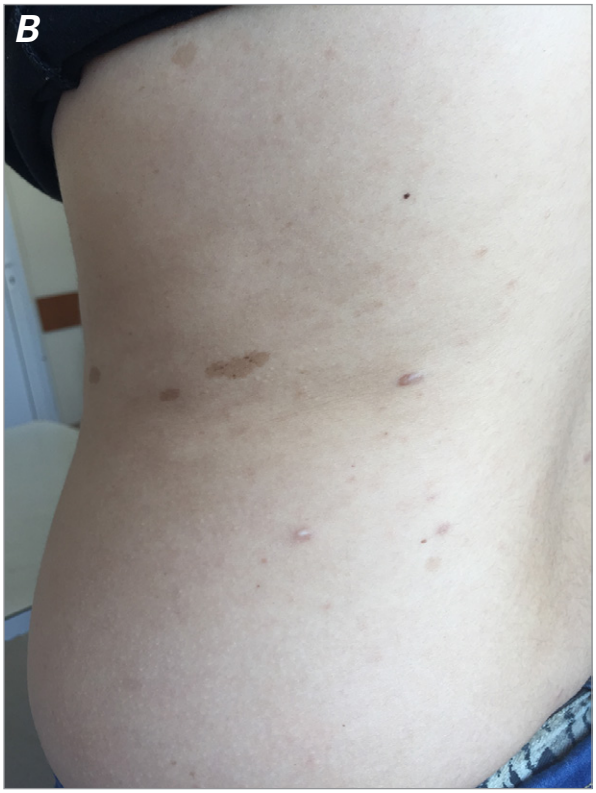

Fig. 1 *Photographs show* ***A****) a flat, 7.5-cm-diameter, café au lait patch on the patient's left arm; and* ***B****) nodular cutaneous and subcutaneous fibromas on the midaxillary line and posterior thorax.*

tion test results, blood cell counts, urinalysis, and levels of serum electrolytes, thyroid hormones, urinary metanephrine and normetanephrine, plasma normetanephrine and chromogranin A, and neuronal-specific enolase were within normal ranges.

Transthoracic echocardiograms showed normal cardiac structure and function and a normal aortic arch. Abdominal ultrasonograms revealed normal-sized kidneys. Abdominal magnetic resonance angiograms, which showed normal RAs, excluded any adrenal or abdominal mass (Fig. 2). However, the elevated plasma levels of renin and aldosterone suggested a renovascular cause of hypertension. Renal angiograms showed a normal right RA, an extremely tortuous left RA with a hemodynamically significant 70%-to-80% stenosis in the mid segment, and a small saccular pseudoaneurysm immediately after the stenosis (Fig. 3). Magnetic resonance angiograms of the head and chest revealed no other vascular abnormalities. The diagnosis was NF1, based on 4 of 7 specific clinical features: optic nerve glioma on computed tomography, café au lait spots, nodular neurofibromas, and axillary freckling.[4]

For one month, the patient took an angiotensin-converting enzyme inhibitor, a calcium channel blocker, a β-blocker, and diuretic agents. These failed to control her BP, so RA angioplasty was scheduled.

During the procedure, we found a 90% stenosis in the left RA (Fig. 4A). We intubated the RA with a coronary Judkins Right 3.5 catheter and crossed the lesion with use of a 0.014-in hydrophilic HI-TORQUE® Pilot 50® guidewire (Abbott Vascular, part of Abbott Laboratories; Redwood City, Calif). Because of the anatomy of the RA and the substantial difference in vessel diameter proximal to the lesion versus distal from it, we decided to deploy a 3.5–4.5 × 27-mm, self-expanding, drug-eluting STENTYS® coronary stent (Stentys SA; Paris, France). We predilated the lesion with a 4 × 20-mm balloon. After stent implantation, an angiogram revealed RA patency in the affected area, and the pseudoaneurysm was closed (Fig. 4B).

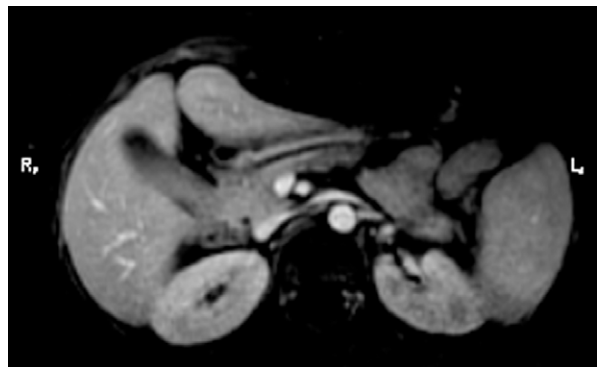

Fig. 2 *Magnetic resonance angiogram (post-contrast T1-weighted arterial time image, in axial view) shows an apparently normal left renal artery emerging from the aorta.*

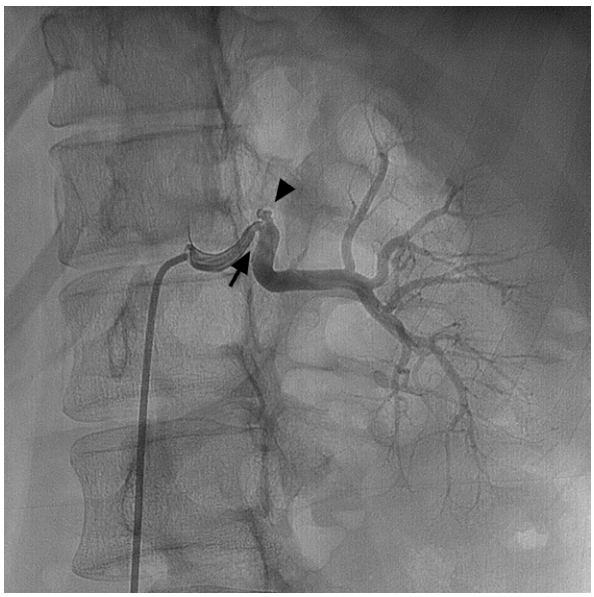

Fig. 3 *Renal angiogram shows extreme tortuosity and a 70%-to-80% stenosis in the mid segment of the left renal artery (arrow), poststenotic dilation of the vessel, and a small saccular pseudoaneurysm immediately after the stenosis (arrowhead).*

Within 48 hours, the patient's BP decreased to normal levels, and she was discharged from the hospital. Her antihypertensive medication was reduced to metoprolol (50 mg/d) and perindopril (5 mg/d), along with dual antiplatelet therapy consisting of aspirin (75 mg/d and clopidogrel (75 mg/d).

One month after revascularization, the patient underwent a careful clinical examination along with 24 hours of ambulatory BP monitoring. Her BP was within normal range, so the medical therapy was discontinued. As of November 2016, she had consistently normal BP (average, <135/80 mmHg on 24-hr monitoring) and renal function, without antihypertensive therapy.

Discussion

Renovascular hypertension caused by RA stenosis leads to progressively impaired renal function and refractory hypertension.[5] The pathologic condition affects patients of all ages and can easily be missed, especially in young patients. Undiagnosed RA stenosis can lead to a poor prognosis with respect to renal function and cardiovascular risk.

Neurofibromatosis type 1, an autosomal dominant disorder, is caused by mutations in the *NF1* gene that are frequently associated with hypertension in young patients.[2] Renal artery stenosis typically causes the hypertension; other causes are aortic coarctation and pheochromocytoma.[6] Although vascular abnormalities such as stenoses, aneurysms, and arteriovenous malformations are frequently found in patients with NF1

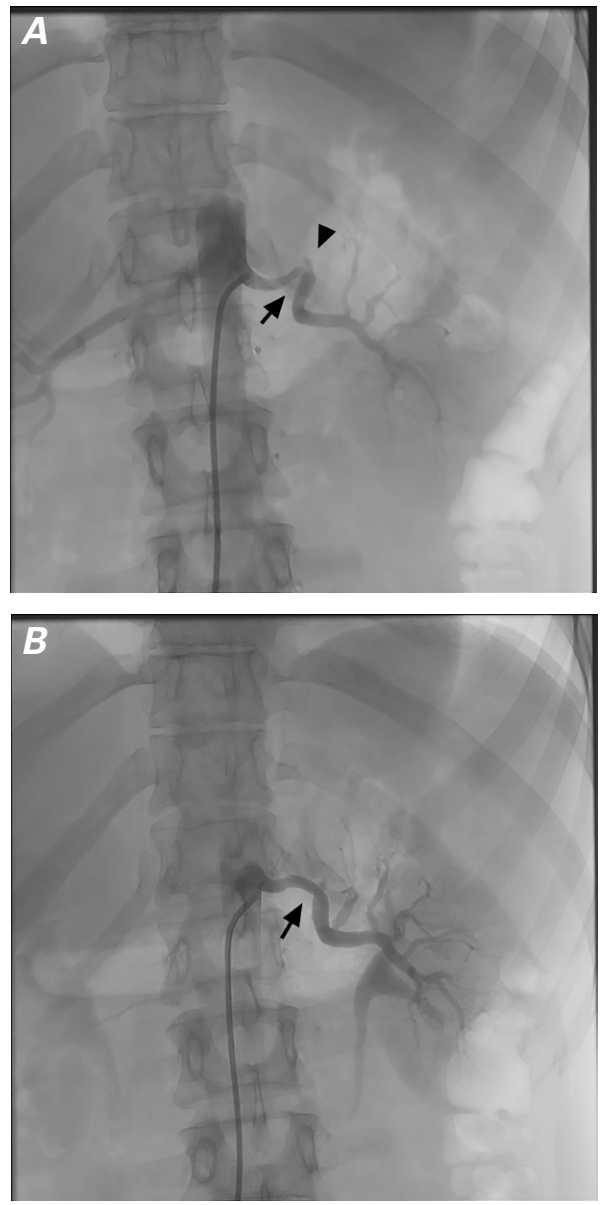

Fig. 4 *One month after initial presentation, renal angiograms show* ***A****) a 90% left renal artery stenosis (arrow) and a saccular pseudoaneurysm (arrowhead), and* ***B****) the successful outcome of left renal artery angioplasty upon implantation of a self-expanding, drug-eluting stent (arrow).*

and suggest a poor prognosis, the pathogenesis of vascular involvement is still under investigation.[3] Arterial stenoses or aneurysms in these patients might develop through a complex process of cellular proliferation, degeneration, healing, smooth-muscle loss, and fibrosis caused by a deficiency in neurofibromin within the endothelium and smooth-muscle cells of the arterial wall.[3]

The current consensus is that noninvasive diagnostic imaging of the RA should be considered first, when RA stenosis is clinically suspected. However, when clinical suspicion is high and noninvasive tests fail to identify

RA stenosis, conventional invasive angiography is the method of choice to establish the diagnosis.[7]

We found no reports about the accuracy of noninvasive diagnostic tests to detect RA stenosis in NF1 patients who have renovascular hypertension. Difficulties in interpreting these diagnostic tests are not surprising, considering the morphologic complexity of the arterial lesions caused by possibly coexistent multiple forms of NF1 vasculopathy. Accordingly, the NF1 Cardiovascular Task Force recommended renal arteriography as the conclusive test for RA stenosis in patients with NF1 and hypertension, and magnetic resonance angiography as the alternative when conventional angiography is not tolerated.[8]

In our patient, renal angiograms revealed anatomic features of RA involvement that magnetic resonance angiograms had not: the tortuous left RA with a focal mid-segment stenosis, poststenotic vessel dilation, and a small saccular aneurysm. The inconclusive results from magnetic resonance might be explained by the superposition of different anatomic elements, thus justifying renal angiography as the preferred diagnostic test in this patient with NF1 and hypertension.[8]

Unlike fibromuscular dysplasia, which usually involves the distal two thirds of the RA, the vasculopathy in neurofibromatosis is proximal in 50% of cases.[9] The aneurysmal dilation with focal stenosis in the mid segment of our patient's main left RA coincides with the general profile of RA involvement in NF1.[3] However, the rapid progression of RA stenosis—from 70% to 90% in one month—was unexpected. The progression of vasculopathy in NF1 is well known and is the main cause of death in these patients.[3] However, to our knowledge, there are no data on the rate of progression of vascular disease.

Treatments for renovascular hypertension secondary to NF1 include drug therapy, percutaneous transluminal renal angioplasty (PTRA), and surgery. Medical therapy to control hypertension is suggested as the initial approach in younger patients, to enable normal body growth before invasive intervention.[10] However, progressive end-organ damage can occur in children when medical control of BP fails.[10] Early investigators reported good results with surgical revascularization in patients with NF1 and renovascular hypertension that did not respond to drugs.[3,11]

Percutaneous transluminal renal angioplasty has emerged as an effective and safe treatment for hypertension caused by RA stenosis. In children with NF1, however, a rather low success rate of 33% has been reported.[12] Higher success rates of 70% were reported in patients with NF1 who had unilateral single lesions.[13,14] The role of PTRA in renovascular hypertension was debatable after the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) investigators[15] failed to find significant differences in adverse cardiovascular and renal events in stent-treated versus untreated patients; however, those results might not fully apply to everyone with RA stenosis because of retrospectively revealed study limitations.

Current class I recommendations for percutaneous renal revascularization pertain to patients with RA stenosis (of any cause) who present with sudden, unexplained "flash pulmonary edema" or recurrent congestive heart failure. However, patients with refractory, accelerated, malignant hypertension (resistant to 3 classes of antihypertensive drugs, including diuretic agents) can also benefit from RA stenting (Class II, evidence level A).[7]

There are no treatment guidelines for RA stenosis in NF1 patients and relatively scanty long-term follow-up data after PTRA. Therefore, in accordance with the current RA stenosis guidelines, renal angioplasty should be performed when clinically indicated.[7]

After medical therapy failed, we decided to perform PTRA in our patient because of its reported effectiveness in isolated renal lesions and low complication rates even in complex lesions, as well as the potential for safe surgery if PTRA were to fail.[16] We implanted a self-expanding, drug-eluting stent because of the RA's anatomic complexity (tortuosity, aneurysm, and poststenotic dilation), the lesion's firmness, and transmural pathologic changes in the arterial wall that could have hampered optimal expansion. Technically and clinically, the patient responded well to angioplasty. At all follow-up evaluations, she had normal BP and renal function without the need for antihypertensive medication.

In our opinion, PTRA can be a valuable adjunct to medical therapy and an alternative to surgery in carefully selected patients with NF1. Moreover, PTRA requires no surgical incisions, reducing morbidity and shortening hospital stays.

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