IMAGING TEACHING CASE

# Midaortic Syndrome in Neurofibromatosis Type 1 Resulting in Bilateral Renal Artery Stenosis

*Imran Saif, MD,[1] Dare Seriki, MD,[2] Roger Moore, MD,[3] and Alexander Woywodt, MD, FRCP[1]*

We describe the case of a 23-year-old white woman with a long history of hypertension. She was referred to us 7 years after her initial diagnosis of hypertension when her blood pressure control worsened during pregnancy. Clinical examination showed an abdominal bruit and weak femoral pulses. Imaging showed midaortic syndrome with bilateral renal artery stenosis as the cause of her hypertension, and further investigations showed neurofibromatosis type 1 as the underlying disorder. Midaortic syndrome, a rare disorder of the abdominal aorta that is different from classic coarctation, typically is associated with neurofibromatosis. Renal artery stenosis is common, as are weak femoral pulses and impaired development of the lower limbs. Because of the rarity of this syndrome, only anectodal evidence exists with regard to treatment. Surgery and interventional treatment with stent placement in the abdominal aorta have been reported, as well as good outcomes with long-term medical management. Our patient continues to be healthy without intervention, with reasonable blood pressure control and normal kidney function on a 4-drug antihypertensive regimen. We discuss midaortic syndrome with a focus on diagnosis, differential diagnosis, associated conditions, and management. Nephrologists, radiologists, and ultrasonographers should be aware of this rare cause of renovascular hypertension.
*Am J Kidney Dis* xx:xxx. *© 2010 by the National Kidney Foundation, Inc.*

***INDEX WORDS:*** Midaortic syndrome; renal artery stenosis; neurofibromatosis; hypertension.

## INTRODUCTION

Renovascular disease is a well-described cause of secondary hypertension. Eighty percent of cases are caused by atherosclerotic renal artery stenosis, whereas the remaining 20% are caused by fibromuscular dysplasia and a number of other uncommon disorders (Box 1).[1] Midaortic syndrome, a congenital disease of the aorta and its branches, is a very rare cause of renovascular hypertension. The disease is different from classic coarctation of the aorta and involves diffuse and irregular narrowing of a segment of the abdominal aorta, often with concomitant stenosis of renal and/or mesenteric arteries. We describe a young woman who presented with severe hypertension and normal kidney function. Imaging showed midaortic syndrome with bilateral renal artery stenosis. Further investigation led to a diagnosis of neurofibromatosis type 1, a disease associated with midaortic syndrome. We describe the case with emphasis on imaging and provide a brief review of midaortic syndrome.

## CASE REPORT

### Clinical History and Initial Laboratory Data

A 23-year-old white woman was evaluated for a history of severe hypertension. She was first found to be hypertensive 7 years earlier when she started experiencing headaches. Blood pressure control had always been difficult despite 3-4 antihypertensive medications. During a recent successful pregnancy, her blood pressure had to be controlled with high doses of labetalol. She was now using amlodipine, 5 mg, and bisoprolol, 2.5 mg, once daily.

The patient had no other medical history of note. She worked as a waitress and did not report illicit drug intake. None of her family members had hypertension or kidney disease, but her mother had neurofibromatosis type 1.

On examination, she was slim and appeared healthy, with blood pressure of 176/112 mm Hg. There was no cardiac murmur and the chest was clear on auscultation. Femoral pulses were weak, and both dorsalis pedis and posterior tibial pulses were absent on Doppler examination. She had an abdominal bruit. There were two 1 × 1-cm pinkish elevated nodules on her anterior abdominal wall. There were no other skin lesions. Serum creatinine level was 0.79 mg/dL (70 $\mu$mol/L) with an estimated glomerular filtration rate of 90 mL/min/1.73 m$^2$ (1.5 mL/s/1.73 m$^2$), calculated using the 4-variable Modification of Diet in Renal Disease

*From the Departments of [1]Nephrology, [2]Radiology, and [3]Cardiology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK.*

*Received January 19, 2010. Accepted in revised form April 20, 2010.*

*Address correspondence to Alexander Woywodt, MD, FRCP, Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Preston PR2 9HT, UK. E-mail: alex.woywodt@lthtr.nhs.uk*



*0272-6386/10/xx0x-0001$36.00/0*
*doi:10.1053/j.ajkd.2010.04.023*

**Box 1.** Causes of Renovascular Hypertension

- Atherosclerotic renal artery stenosis
- Fibromuscular dysplasia
- Arteriovenous malformation
- Thrombosis or embolism of the renal artery
- Cholesterol emboli disease
- Renal artery trauma
- Renal artery aneurysm
- Takayasu arteritis
- Aortic dissection with ostial involvement of the renal arteries
- Polyarteritis nodosa
- Giant cell arteritis
- Midaortic syndrome
- External compression of the kidney (Page kidney)
- Aortic thrombosis (Leriche syndrome)

Source: Textor.[1]

(MDRD) Study equation, modified for isotope dilution mass spectrometry (IDMS). Serum potassium level was 4.3 mEq/L (4.3 mmol/L), and C-reactive protein level was normal.

## Imaging Studies

On ultrasonographic examination, the right kidney was 103 mm and the left kidney was 97 mm, with preserved parenchymal thickness and smooth outlines bilaterally. There was no hydronephrosis. The resistive index in distal segmental arteries was low bilaterally (0.48 on the right and 0.52 on the left side). The abdominal aorta had a funnel-like narrowing distal to the origin of the renal arteries, with a decrease in aortic diameter from 12.5 to 7.2 mm (Fig 1). A concomitant increase in blood velocity in the aorta from 190 to 564 cm/s was noted. Aliasing in both proximal renal arteries was noted (maximum velocities in the right and left renal arteries were 453 and 740 cm/s, respectively). Magnetic resonance angiography confirmed tapering of the aorta at the level of the renal arteries, with a diffusely narrowed irregular infrarenal portion of aorta from just below the origin of renal arteries to the aortic bifurcation (Fig 2). Computed tomographic angiography (CTA) of the abdomen was performed, which excluded external compression of the abdominal aorta by neurofibroma. The origins of both renal arteries showed significant stenosis, more severe on the left side (Fig 3A). There also was stenosis at the origin of the superior mesenteric artery (Fig 3B; Movies S1 and S2, provided as online supplementary material associated with this article at www.ajkd.org).

## Diagnosis

The imaging diagnosis was midaortic syndrome with stenosis of the bilateral proximal renal arteries and superior mesenteric artery. A clinical diagnosis of neurofibromatosis type 1 was made on the basis of 2 neurofibromas and a first-degree relative with the disease.[2]

## Clinical Follow-up

The patient continues to be healthy, and her kidney function has remained normal (serum creatinine, 0.81 mg/dL [71 $\mu$mol/L]; estimated glomerular filtration rate, 86 mL/min/1.73 $m^2$ [1.4 mL/s/1.73 $m^2$]). She currently uses amlodipine, 10 mg; nebivolol, 5 mg; moxonidine, 400 $\mu$g; and doxazosin, 4 mg, daily. Home blood pressures are 130/85-140/90 mm Hg, and there are no side effects from these drugs. A human geneticist confirmed our clinical diagnosis of neurofibromatosis and believed that genetic testing was not required.

**Figure 1.** Power Doppler ultrasound of the abdominal aorta (longitudinal axis) shows funnel-like narrowing.

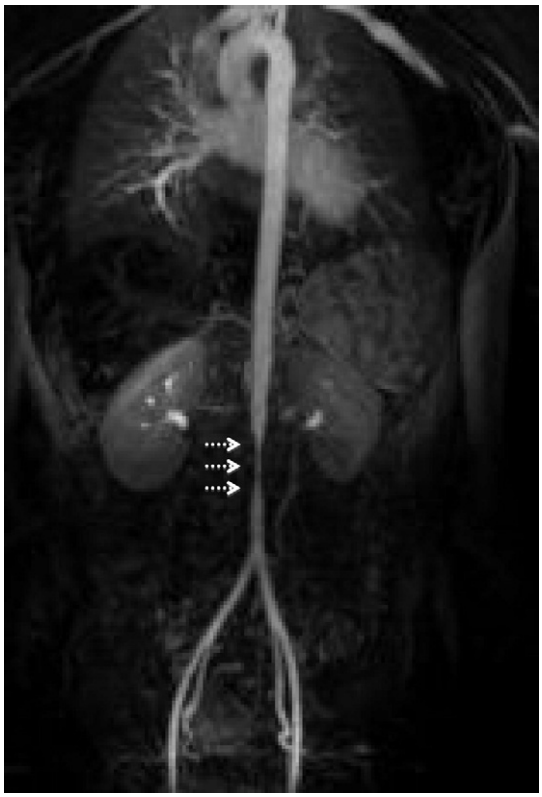

**Figure 2.** Magnetic resonance angiogram of the abdominal aorta shows the irregular aortic narrowing typical of the midaortic syndrome (dotted arrows) and bilateral renal artery stenosis.

## DISCUSSION

Renovascular hypertension usually is caused by atherosclerotic disease of the renal arteries or, less commonly, fibromuscular dysplasia. Rare causes of renovascular hypertension are discussed elsewhere[1] (Box 1). In the young woman described here, fibromuscular dysplasia was a tempting diagnosis until imaging showed the funnel-like narrowing of the abdominal aorta.

Initially described in 1835 by Dr Schlessinger as a subisthmic coarctation, midaortic syndrome was reported in its current form by Sen et al[3] in 1963. It is characterized by segmental narrowing of the abdominal aorta. The irregular and diffuse nature of the narrowing, as well as the unique location, differentiate it from simple aortic coarctation, which typically involves a short segment just distal to the left subclavian artery. In contrast, midaortic syndrome can affect the supra-, inter-, or infrarenal portion of the abdominal aorta with a >60% chance of associated renal artery stenosis.[4] Other conditions that can mimic midaortic syndrome are giant cell arteritis, Takayasu arteritis, fibromuscular dysplasia, and retroperitoneal fibrosis.[5] In our case, the absence of systemic symptoms and signs, normal C-reactive protein level, and smooth outline of the aorta on cross-section images gave us confidence to exclude giant cell arteritis and Takayasu arteritis. Furthermore, fibromuscular dysplasia usually affects the distal two-thirds of the renal artery, whereas in midaortic syndrome, >50% of all stenoses are at the origin,[6] as was the case here. Also, the lesions in our patient lacked the typical "string-of-pearls" appearance of fibromuscular dysplasia. Finally, external compression by neurofibromas or retroperitoneal fibrosis was excluded using repeated CTA.

The cause of midaortic syndrome is not clear; however, the association with neurofibromatosis

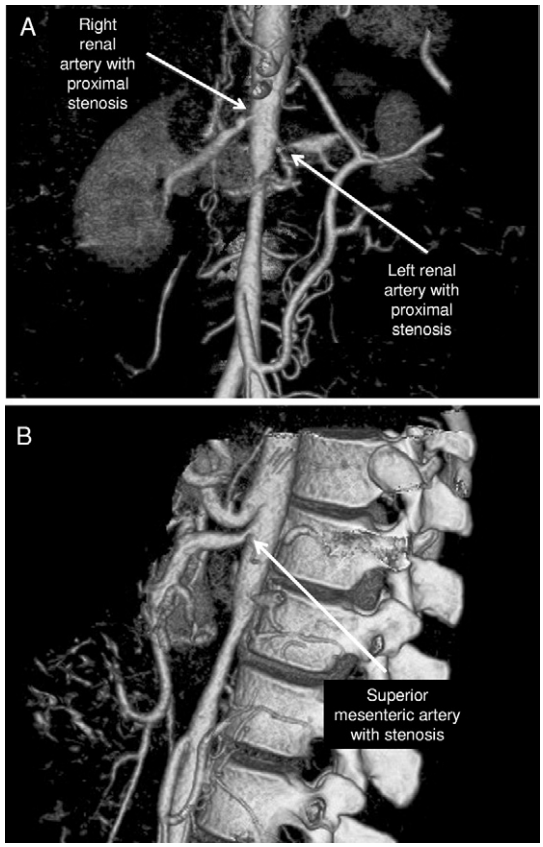


**Figure 3.** Three-dimensional reconstruction of the abdominal aorta and renal arteries based on computed tomographic angiography. (A) Anterior view shows aortic narrowing with bilateral renal artery stenosis. (B) Sagittal view shows stenosis of the superior mesenteric artery.

suggests a genetic background. It has been proposed that a primarily underdeveloped segment of the abdominal aorta, including the proximal portion of the renal arteries, is the hallmark of the disease. Histologically, there is marked subendothelial fibroplasia without inflammation.[7]

Cases come to light either during the evaluation of hypertension or because of claudication of the lower limbs. The diagnosis also may be an incidental finding during abdominal ultrasonography. This supports the need to visualize the abdominal aorta in a longitudinal axis during routine abdominal ultrasonography. Hypertension often is difficult to control despite multiple antihypertensive agents and may lead to significant end-organ damage. Failure to thrive also is common, as is underdevelopment of the legs.[8] Clinical examination shows higher blood pressure in the arms than the legs and weak femoral pulses, occasionally with an abdominal bruit. The natural history of midaortic syndrome is not well described because of the rarity of the disease. In children, a mortality rate of 8% after 4.5 years has been described in a single-center experience with 36 children.[9]

In our case, midaortic syndrome was associated with neurofibromatosis type 1, which is a well-described association. The presence of skin lesions of neurofibromatosis type 1 along with a family history helped clinch the diagnosis.[10] In children, renovascular disease is the third most common cause of secondary hypertension after renal scarring and glomerulonephritis.[7] In children with neurofibromatosis type 1 in a recent case series, 18.5% were hypertensive, with renovascular disease as the leading secondary cause.[4] Another rare cause of hypertension in patients with neurofibromatosis type 1 is pheochromocytoma.[11] An entire range of vascular abnormalities can be seen in those with neurofibromatosis type 1,[12] and midaortic syndrome may be one phenotype within this spectrum. Interestingly, a retrospective study of 31 patients with clinical neurofibromatosis type 1 showed that although mean age at diagnosis of neurofibromatosis type 1 was 11 $\pm$ 10 years, vascular lesions were not identified until a mean age of 38 $\pm$ 16 years.[12] It is unclear why these vascular lesions take so long to develop.

CTA and magnetic resonance angiography are both appropriate to diagnose midaortic syndrome. In this case, both were performed. CTA served to exclude direct involvement of the aorta by neurofibromas. It also is conceivable that an instant diagnosis of the disorder is made during routine abdominal ultrasonography. This would require visualization of the abdominal aorta in a longitudinal view, as well as knowledge of the disease. Hence, radiologists and radiographers also should be aware of the disease. CTA also excludes the rare possibility of neurofibromas causing external compression of the aorta. From an imaging point of view, the differential diagnosis includes large-vessel vasculitis, such as giant cell arteritis or Takayasu arteritis, fibromuscular dysplasia, the mucopolysaccharidoses, and congenital rubella syndrome. Here, the absence of inflammatory markers gave us confidence to exclude vasculitis. In patients with fibromuscular dysplasia, the renal arteries usually show the typical string-of-pearls involvement and not the proximal involvement seen in the patient under discussion. Also, fibromuscular dysplasia usually does not involve the abdominal aorta, whereas both fibromuscular dysplasia and midaortic syndrome share the propensity to also affect the mesenteric arteries. Our patient had stenosis of the superior mesenteric artery, but this was entirely asymptomatic. These considerations, as well as the well-described association with neurofibromatosis type 1, gave us further confidence to arrive at a diagnosis of midaortic syndrome.

There is little evidence to guide treatment in midaortic syndrome. Surgical options[5] include aorto-aortic bypass, patch aortoplasty, bypass grafting of the stenosed renal and visceral arteries, and autotransplant of the kidneys, usually with a saphenous graft.[13] A study of 8 patients with midaortic syndrome who underwent vascular surgery included follow-up of 4-9 years and showed patency of all grafts postoperatively and well-controlled blood pressure.[14] That many patients are children mandates that surgical and interventional options are weighed carefully against the risks of such intervention while the aorta is still growing.[11] In some cases, the occlusive process may progress despite surgery and necessitates close follow-up of these patients.[12] Angioplasty with stent placement in the abdominal aorta also has been described[15] and may be an option in carefully selected patients. In this

series, eight atherosclerotic stenoses of the infrarenal aorta and one case of midaortic syndrome underwent stent placement, which was technically successful and not associated with complications; patency was excellent during follow-up. The authors proposed that stenting of the infrarenal aorta is feasible and safe.[15] Others have reported poor results using angioplasty.[7] Medical management is another option, and our patient continues to do well using 4 antihypertensive drugs.

In conclusion, we report a young woman with severe hypertension caused by midaortic syndrome due to neurofibromatosis type 1. The family history of neurofibromatosis could have been a clue to suggest an unusual cause of hypertension. Nephrologists and radiologists should be aware of midaortic syndrome as a rare cause of renovascular hypertension.

## ACKNOWLEDGEMENTS

We thank Professor Yanick Crow, Human Genetics Unit, St Mary's Hospital, Manchester, UK, for help with the clinical diagnosis of neurofibromatosis.

*Support:* None.

*Financial Disclosure:* The authors declare that they have no relevant financial interests.

## SUPPLEMENTARY MATERIAL

Movie S1: Three-dimensional reconstruction of abdominal aorta and renal arteries based on computed tomographic angiogram.

Movie S2: Three-dimensional reconstruction of abdominal aorta and renal arteries based on computed tomographic angiogram (higher magnification).

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.04.023) is available at www.ajkd.org.

## REFERENCES

1. Textor SC. Current approaches to renovascular hypertension. *Med Clin North Am*. 2009;93(3):717-732.

2. Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann Intern Med*. 1990;113(1):39-52.

3. Sen PK, Kinare SG, Engineer SD, Parulkar GB. The middle aortic syndrome. *Br Heart J.* 1963;25:610-618.

4. Fossali E, Signorini E, Intermite RC, et al. Renovascular disease and hypertension in children with neurofibromatosis. *Pediatr Nephrol.* 2000;14(8-9):806-810.

5. Delis KT, Gloviczki P. Middle aortic syndrome: from presentation to contemporary open surgical and endovascular treatment. *Perspect Vasc Surg Endovasc Ther*. 2005;17(3):187-203.

6. Schurch W, Messerli FH, Genest J, et al. Arterial hypertension and neurofibromatosis: renal artery stenosis and coarctation of abdominal aorta. *Can Med Assoc J.* 1975;113(9):879-885.

7. Lin YJ, Hwang B, Lee PC, Yang LY, Meng CC. Mid-aortic syndrome: a case report and review of the literature. *Int J Cardiol.* 2008;123(3):348-352.

8. Criado E, Izquierdo L, Lujan S, Puras E, del Mar Espino M. Abdominal aortic coarctation, renovascular, hypertension, and neurofibromatosis. *Ann Vasc Surg.* 2002;16(3):363-367.

9. Tummolo A, Marks SD, Stadermann M, et al. Midaortic syndrome: long-term outcome of 36 children. *Pediatr Nephrol.* 2009;24(11):2225-2232.

10. Ferner RE. Neurofibromatosis 1. *Eur J Hum Genet.* 2007;15(2):131-138.

11. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. *J Urol.* 1999;162(5):1582-1586.

12. Oderich GS, Sullivan TM, Bower TC, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. *J Vasc Surg*. 2007;46(3):475-484.

13. Bleacher J, Turner ME, Quivers E, Schwartz MZ. Renal autotransplantation for renovascular hypertension caused by midaortic syndrome. *J Pediatr Surg.* 1997;32(2):248-250; discussion 250-251.

14. Connolly JE, Wilson SE, Lawrence PL, Fujitani RM. Middle aortic syndrome: distal thoracic and abdominal coarctation, a disorder with multiple etiologies. *J Am Coll Surg.* 2002;194(6):774-781.

15. Stoeckelhuber BM, Stoeckelhuber M, Gellissen J, Kueffer G. Primary endovascular stent placement for focal infrarenal aortic stenosis: long-term results. *J Vasc Interv Radiol.* 2006;17(7):1105-1109.