Balancing Overscreening and Underdiagnosis in Secondary Hypertension

The Case of Fibromuscular Dysplasia

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KEYWORDS

• Secondary hypertension • Renovascular hypertension • Fibromuscular dysplasia • Hypertension • Screening • Renal artery stenosis

KEY POINTS

- The prevalence of fibromuscular dysplasia (FMD) is higher than originally thought.
- FMD affects the extrarenal vascular bed nearly as frequently as it affects the renal arteries.
- Symptoms of extrarenal FMD can be vague and nonspecific.
- Low awareness of extrarenal FMD by physicians and patients results in delayed diagnosis and missed opportunity to prevent catastrophic vascular events.
- Adverse outcomes of undiagnosed and untreated extrarenal FMD are debilitating and life threatening.

INTRODUCTION

Historical Perspective

The discovery of the role of the renal artery and hypertension dates back to the first half of the twentieth century. Experiments by Goldblatt and colleagues[1] established that narrowing of the renal artery, resulting in significant impairment of renal blood flow, induces renal renin and leads to arterial hypertension. Because treatment of severe hypertension at that time was limited principally to extreme dietary salt restriction and dorsal lumbar sympathectomy, alternative surgical treatment (in this case renal autotransplant and/or bypass of the affected renal artery) provided a reasonable treatment option for patients with renal artery stenosis. However, it became clear, even at the early stages, that not all stenoses of the renal artery were the same with regard to cause. In addition to atherosclerotic renal artery stenosis, Leadbetter and Burkland[2] in 1938 reported cure of hypertension in response to unilateral nephrectomy in a

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5.5-year-old boy with severe hypertension and a renal artery partially occluded by a prominent intra-arterial mass of smooth muscle. The term fibromuscular dysplasia (FMD) was first used in the setting of hypertension and renal artery stenosis by McCormack and colleagues in 1958.[3] During the following decade, FMD was recognized in extrarenal territories, including cerebrovascular (carotid and vertebral arteries), mesenteric arteries, arteries of upper and lower extremities, and coronary arteries. Harrison and McCormack[4] proposed a histologic classification of 3 distinct types of FMD based on the arterial layer most affected: intimal, medial, and adventitial/periarterial. Over the years, the most common adverse features of the natural history of FMD, such as arterial stenosis/occlusion, dissection, and aneurysm, were recognized. Clinical manifestation of these based on the part of the arterial tree involved were described. Treatment options evolved from surgical revascularization and clipping of aneurysms to catheter-based (angioplasty with/without stenting for stenosis, stents for dissections, and coils and stents for aneurysms) and medical management (antiplatelet, antithrombotic, and antihypertensive therapy, and lifestyle modification).[5]

Progress, and the Lack of It, over the Last 8 Decades

Thus, clearly, over the last several decades, major progress has been made with regard to the ability to diagnose FMD and management options to prevent catastrophic vascular outcomes. In contrast, a comprehensive review on FMD by Plouin and colleagues[6] was published as recently as in 2007 in the *Orphanet Journal of Rare Disease*, highlighting the still limited awareness of FMD by physicians and patients. In 2014, a Scientific Statement from the American Heart Association on Fibromuscular Dysplasia, published in *Circulation*, indicated that "an average delay from the time of the first symptom or sign to the diagnosis of FMD is 4 to 9 years."[7] As highlighted by the case presented later in this article, this delay or even a missed diagnosis of FMD can lead to catastrophic vascular outcomes. This article solely focuses on 2 major features crucial to the case presented later; namely the nonspecific signs and symptoms of this disease, and its prevalence in extrarenal vascular beds, which, in contrast with the older dogma of being extremely rare, is nearly equal to its occurrence in renal arteries.

Case report

A 34-year-old woman was referred to the renal hypertension clinic, from the stroke rehabilitation unit, for assessment of hypertension, specifically to consider secondary hypertension. She was recovering from a left hemiparesis, associated with a right internal carotid artery dissection, and her blood pressure in the rehabilitation unit was persistently high (>180/110 mm Hg) despite 3 antihypertensive agents. Urinary catecholamines had been done and found to be high, hence the referral was made to investigate and treat for pheochromocytoma.

She was first diagnosed to have high blood pressure when she was 30 years old, during her first (and only) pregnancy. She was started on an antihypertensive medication, but did not recall how well her blood pressure was controlled. She had been a smoker until then, and quit smoking, as well as losing 18 kg (40 pounds) over the next few months in an effort to control blood pressure. Four years after the diagnosis of hypertension, she developed transient blurring of vision and a headache one evening while jogging. The next morning, she developed left-sided hemiparesis and diplopia. Imaging revealed an acute infarct in the right middle cerebral artery (MCA) territory. A computed tomography (CT) angiogram revealed an internal carotid artery dissection, just distal to the bifurcation of the common carotid artery. There was also thrombosis seen in the proximal right MCA. Her course was complicated by cerebral edema and midline shift, requiring a craniotomy, and a subsequent deep venous thrombosis and pulmonary embolism. She required a prolonged rehabilitation stay, during which it was found that the blood pressure was not well controlled despite bisoprolol 5 mg daily, ramipril 2.5 mg daily, and hydrochlorothiazide 25 mg daily. A 24-hour urinary epinephrine was 40 nmol/d (laboratory range for normal, <100 nmol/d), norepinephrine 898 nmol/d (normal, <500), and dopamine 2708 nmol/d (normal, <2600). At the first visit to our clinic, resting blood pressure measurements, performed with an automated monitor, on the same therapy, revealed a blood pressure of 123/81 mm Hg. Serum creatinine level was 58 μmol/L and potassium level was 3.4 mmol/L. There was no proteinuria. Electrocardiogram and echocardiogram did not reveal left ventricular hypertrophy.

Because of the history of carotid dissection, a renal CT angiogram was ordered, which showed that the renal arteries were abnormal with intermittent stenotic and poststenotic ectasia, having a string-of-beads appearance in keeping with FMD. After discussion with the patient about potential benefits and risks, catheter angiogram was performed, which revealed a beaded appearance with multiple webs consistent with FMD within the terminal left renal artery and continuing