Neurofibromatosis type 1-associated hypertension secondary to coarctation of the thoracic aorta

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Abstract
Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is an autosomal dominant genetic disorder. NF-I vasculopathy has been used to describe various vascular malformations associated with NF-1. Secondary hypertension related to NF-1 vasculopathy has been reported because of renal artery stenosis, coarctation of the abdominal aorta and other vascular lesions; however, coarctation of the thoracic aorta has seldom been reported. We report the first case, to our knowledge, of isolated coarctation of thoracic aorta in a pregnant female with NF-1. Healthcare providers caring for patients with NF-1 should be aware of associated vascular complications.

Keywords: aorta; coarctation; NF-1; vasculopathy

Background
Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's disease, is an autosomal dominant genetic disorder, characterized by a mutation of NF-1 gene located on chromosome 17q 11.2. It is known to affect 1 in 4000 individuals at birth [1]. The diagnosis of NF-1 is based on criteria established by the National Institute of Health in 1987 and includes café-au-lait macules, intertriginous freckling, dermal neurofibroma, iris hamartoma (Lisch nodules), optic glioma, distinctive osseous lesions and a first-degree relative with NF-1 [1]. The diagnosis is established by the presence of two or more criteria. The term NF-1 vasculopathy has been used to describe various vascular malformations including aneurysms, stenosis and arteriovenous malformations associated with NF-1 [2]. Secondary hypertension related to NF-1 vasculopathy has been previously reported because of renal artery stenosis (RAS), coarctation of the abdominal aorta and other vascular lesions with renal artery being the most frequent site of involvement [3]. However, coarctation of thoracic aorta has seldom been reported; when it occurs, the diagnosis is usually made in children [4]. Herein, to our knowledge we report the first case of secondary hypertension, related to isolated coarctation of the thoracic aorta.

Case report
A 32-year-old female G1 P0, with a medical history of NF-1 and hypertension, was admitted to our institution for planned termination of pregnancy at 21 weeks of gestation. Post-termination of pregnancy, the patient’s blood pressure readings were consistently more than 200/100 mmHg. The patient denied hematuria, blurry vision, headaches or neurological deficits.

Her physical examination revealed a well-nourished female with widely distributed neurofibromas and café au lait macules on her face, arms and torso. Upon admission, her vital parameters were 160–200/80–120 mmHg and the heart rate was 80–110 ppm. The rest of her examination was unremarkable. She was initially treated with intravenous labetalol 10 mg pushes, as needed, to maintain a blood pressure <170/100 mmHg. She was eventually started on oral labetalol 200 mg every 8 h, hydrochlorothiazide 25 mg and nifedipine extended release tablet 60 mg daily. Despite being on three antihypertensive medications, her blood pressure was still uncontrolled. Investigations were done to exclude secondary causes of hypertension including pheochromocytoma, RAS, hyperthyroidism, primary aldosteronism and Cushing’s disease. Each was ruled out by appropriate testing. A renal ultrasound revealed normal-sized kidneys ∼13 cm each. Renal artery Doppler did not reveal RAS but to confirm, a magnetic resonance angiography of the abdomen was ordered. It revealed focal stenosis of the distal descending thoracic aorta with a luminal diameter of 0.6 cm compared with a luminal diameter of 1.7 cm distal and proximal to the stenotic level, representing coarctation at an unusually low level of the thoracic aorta. A computed tomography angiogram of the chest confirmed focal stenosis of the descending thoracic aorta (Figure 1). Further, the blood pressure measured in all four extremities revealed bilateral upper extremity blood pressure range of 160–170/70–80 mmHg, whereas that of the
lower extremities ranged between 110–120/70–80 mmHg. The pressure gradient across the coarctation was measured to be 59 mmHg. The patient was discharged home in a stable condition on oral labetalol 300 mg every 8 h, hydrochlorothiazide 25 mg daily and nifedipine extended release tablet 90 mg daily with her blood pressure better controlled. Two weeks later, the patient was readmitted and she underwent successful endovascular aortic repair, with stenting, of the thoracic coarctation (Figure 2). The pressure gradient post-stenting decreased to 2 mmHg. The patient was discharged with a well-controlled blood pressure of 120/70 mmHg, on only one agent, labetalol 200 mg every 8 h, along with daily aspirin 81 mg and clopidogrel 75 mg.

Discussion

The NF-1 gene codes for neurofibromin, a tumor-suppressor protein that is widely expressed throughout the body including the brain, kidney and blood vessels [5]. Loss of function of neurofibromin is associated with uncontrolled proliferation or differentiation of endothelial and smooth-muscle cells of the blood vessels, at the cellular level [6]. Consequently, the normal processes of vascular maintenance and repair are altered resulting in intimal thickening and vasculopathy. NF-1-associated vasculopathy, with a prevalence of 0.4–6.4%, is the clinical term that incorporates these various vascular malformations [2], which can be occlusive or aneurismatic and have been reported throughout the entire arterial tree [3].

A retrospective review of 31 patients by Oderich et al. revealed that the diagnosis of NF-1 vasculopathy was identified at a mean age of 38 ± 16 years. The lesions reported include aneurysms, stenoses and arteriovenous malformations (AVM). There were four lesions of coarctation of the abdominal aorta and one of coarctation of thoracoabdominal aorta. Furthermore, in this report, Oderich et al. reviewed the English literature from 1957 through 2005, which revealed 237 patients with NF-1. They identified 320 vascular abnormalities with renal artery lesions being the most prevalent at 41%, whereas coarctation and aneurysms of the abdominal aorta occurred in only 12% of the cases. There were no lesions reported of isolated coarctation of the thoracic aorta [4].

Despite the widespread occurrence of vascular lesions, the incidence of clinically significant vascular lesions in these patients is rare (2%). Hence, routine screening for vasculopathy in NF-1 patients is not recommended. However, if evaluation for secondary causes of hypertension reveals a vascular abnormality, then additional imaging of the head, chest and abdomen is recommended as the patient can have multiple vascular lesions [4].

Conflict of interest statement. None declared.

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