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Neurofibromatosis type 1 (NF1): as a cause of hypertension

Hipertansiyon sebebi olarak Nörofibromatozis Tip 1 (NF1)

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Abstract

Neurofibromatosis type 1 (NF1), an autosomal dominant disorder, is characterized by various clinical manifestations as a result of dysplasia of neuroectodermal and mesodermal tissues. Cafe-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas with a variable clinical expression, iris Lisch nodules, and multiple tumors of central and peripheral nervous system, also other systems may be involved. NF1 patients develop hypertension due to renovascular diseases, mid-aortic syndrome, or pheochromocytoma. In pediatric NF1 patients elevated blood pressure is usually due to renal artery stenosis, generally involving the origin or the proximal tract of the vessel, and is associated in 25% of patients with coarctation of the abdominal aorta. Several patients with NF1 and hypertension have been reported in the literature, showing the extreme variability in anatomical lesions. Although NF1 is a rare disease, it is an important cause of renovasculer hypertension in childhood. Abdominal bruit is an alerting physical finding in diagnosis of renal artery stenosis. We here presented our two cases diagnosed with hypertension while being screened for NF1 to emphasize the importance of blood pressure measurement in children with NF1 screening. Also we suggest that hypertensive NF1 patients should be examined in terms of stenosis in the major branch vessels of the aorta and renal arteries.

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Key words: Neurofibromatosis, hypertension, children.

Özet

Nörofibromatozis tip 1 otozomal dominant geçiş gösteren nöroektodermal ve mezodermal dokuların displazisi sonucu ortaya çıkan klinik bulgular ile karekterizedir. Cafe-au-lait denilen karekteristik pigmente deri lezyonu, aksiller ve inguinal çillenme, deri nörofibromaları, Lisch nodülleri denilen pigmente iris hamartomaları, merkezi sinir sistemi tümörleri, periferik sinir sistemi tümörleri ve diğer sistemleri ilgilendiren tümörler görülebilir. Nörofibromatoz tip 1 de hipertansiyon renovasküler hastalıklar, mid-aortik sendrom veya feokromasitomaya bağlı olarak gelişebilir. Çocukluk yaşlarında nörofibramatoza bağlı hipertansiyonun nedeni genellikle renal arter stenozu olup genellikle damarın proksimalini veya orijini ilgilendirir. Hastaların %25'inde aort koarktasyonu ile birliktedir. Nörofibromatozis nadir görülen bir hastalık olsada çocukluk çağında ki renovasküler hipertansiyonun önemli nedenlerinden biridir. Nörofibramatoz tip 1 nedeniyle izlenirken hipertansiyon tespit edilen iki olgumuzu NF 1 izleminde kan basıncı ölçümleri ile tarama yapılmasının önemini belirtmek ve aort ana dallarının ve renal arterlerin hipertansiyon tespit edilen olgularda stenoz açısından incelenmesinin önemini vurgulamak için sunduk.

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Anahtar sözcükler: Nörofibromatozis, hipertansiyon, çocuk..

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with an incidence of approximately 1:3.000 [1]. This disorder is characterized by various clinical manifestations as a result of dysplasia of neuroectodermal and mesodermal tissues. Cafe-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas with a variable clinical expression, iris Lisch nodules, and multiple tumors of central and peripheral nervous system, also some other systems may be involved.

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NF1 patients develop hypertension due to renovascular diseases, mid-aortic syndrome, or pheochromocytoma [2-4]. Vascular changes may affect vessels of all calibers, but they are most common in the renal arteries, aorta, mesenteric and cerebral arteries [1]. In pediatric NF1 patients, elevated blood pressure is usually due to renal artery stenosis [5-8], generally involving the origin or the proximal tract of the vessel [3,5,6], and is associated in 25% of patients with coarctation of the abdominal aorta [3]. Several patients with NF1 and hypertension have been reported in the literature, showing the extreme variability in anatomical lesions [3,4]. We present two patients with renovascular hypertension in association with neurofibromatosis.

Case 1

A 14 year old girl was admitted to our clinic for the complaints of short stature and cafe-au-lait spots. She was a full term normal delivery without any antenatal or postnatal problems, with a birth weight of 3.6 kg. Her family history was not suggestive of neurofibromatosis. Her medical examination revealed elevated arterial blood pressure of 150/90 mmHg at the upper arm (systolic and diastolic pressures ≥95th percentile for her age and height, stage 2). On her physical examination at our hospital, she weighed 32 kg (<3th percentile) and her height was 140 cm (<3th percentile) and height SDS -3.1, body mass index 16.3 kg/m^2. She also had more than 7 cafe-au-lait spots larger than 1.5 cm and axillary freckling. Her cardiac auscultation was normal and had a normal pulse in the upper and lower extremities. Other systemic examinations were unremarkable.

Clinical diagnosis of NF1 requires the presence of at least 2 of 7 criteria to confirm the presence of NF1 which are as follows: Six or more cafe-au-lait spots or hyperpigmented macules ≥5 mm in diameter in children younger than 10 years and to 15 mm in adults, axillary or inguinal freckle, two or more typical neurofibromas or one plexiform neurofibroma, optic nerve glioma, Two or more iris hamartomas (Lisch nodules, sphenoid dysplasia or typical long-bone abnormalities, first-degree relative with NF1. Our patient was diagnosed as NF1 as having six cafe-au-lait spots ≥1.5 cm in diameter and axillary freckle. A computed tomographic scan of her head displayed hamartomatous lesions at pons and globus pallidus. Renal function tests and renal Doppler ultrasound scan were normal. Echocardiography showed left ventricular and interventricular wall thickness increase and mitral valve regurgitation.

24-hour ambulatory blood pressure monitoring revealed daytime systolic blood pressure load 80% and diastolic blood pressure load 50% and night time systolic blood pressure load 73% and diastolic blood pressure load 46%. Both systolic and diastolic blood pressures were non-dipper.

The hypertension was treated with oral amlodipine and verapamil in total daily doses of 10 mg and 120 mg a day respectively. High doses of medication improved, but did not normalize his blood pressure that's why renovascular reasons were thought. Plasma renin activity was 4 ng/ml/hr (normal < 0. 5-3. 3).

A computerized tomographic angiography showed that there were proximal abdominal aorta stenosis, with 7.5 mm segment of complete obstruction without a lumen and also stenosis of *truncus coeliacus.* No adrenal lesions were noted. Right renal artery originated distal to obstructed aorta segment with normal caliber. Left renal artery located cranially was severely stenotic while the contralateral distal renal artery was normal. The evidence of end-organ dysfunction was investigated. Grade 1 hypertensive retinopathy was diagnosed. Left ventricular mass index was increased to 30.95 gr/m^2. There were no microalbuminuria, and glomerular filtration rate was normal, both of which are easily measured parameters. The systolic augmentation index (sAix), calculated from the central aortic pulse wave (reconstructed from the noninvasive recording of the radial pulse with applanation tonometry), and widely used as a simple index of central arterial stiffness was index 16% (normal <10%). He had normal *pulse wave velocity* (PWV) 4.1 m/sn (normal <5 m/sn), but increased carotid intima media thickness 0.68 mm (normal <0.5 mm).

Case 2

A six-year-old Caucasian boy presented to the orthopedics clinic with pain in her left cruris following minor trauma. We consulted and transferred patient to our department because of hypertension. He was a full-term normal delivery without any antenatal or postnatal complications with a birth weight of 2.7 kg. A month before admission, he was operated for left tibia fracture. His motor and mental development was normal. She had a strong family history of NF-1, her mother and father exhibited clinical features. Medical examination revealed elevated arterial blood pressure of 156/95 mmHg at the upper arms, according to TASK FORCE stage 2 hypertension. On physical

examination at our hospital, she weighed 23. 6 kg (75-90 th percentile), her height was 120 cm (75 th percentile). Body mass index 15 kg/m^2, he had 3 cafe-au-lait at both lower and upper extremities lower than 1. 5 cm.

Bilateral femoral tracings were taken; loud grade 3/6 systolic ejection murmur could also be heard over the abdominal aorta. Other systemic examinations were unremarkable. She had clinical diagnosis of NF1 as having six cafe-au-lait spots, axillary freckle and first-degree relative with NF1.

Complete cell count, blood urea nitrogen, creatinine, and electrolyte levels of blood, lipid profile were all within normal limits. Her thyroid function tests, urinary vanillyl mandelic acid (VMA) level were within normal range. Renal doppler ultrasonography showed left small kidney of 5th percentile. She had no sign of hypertensive retinopathy and albuminuria. Elevated left ventricular mass was 38gr/m^2 on echocardiography.

24-hour ambulatory blood pressure monitorization showed daytime systolic blood pressure load 43% and and night time systolic blood pressure load 94% and both systolic and diastolic pressure were non-dipper. The systolic augmentation index (sAix), calculated from the central aortic pulse wave was increased to 21%, and also Pulse Wave Velocity was increased to 5.8 m/sn Carotids intima media thickness (0.68 mm) and high sensitive CRP was high.

The hypertension treatment was started with oral amlodipine but unsuccessful in control of her blood pressure and doxazosin was added. The patient had stage 2 hypertension angiotensin inhibitors (ACEİ) and angiotensin receptor blocker (ARB) were given to control BP. High doses of multiple medication were needed for renovascular reasons were thought. Plasma renin activity was investigated and found 0.9 ng/ml/hour (normal < 0.5-5.9).

At the fifth day of the treatment renal functional tests were worsened urea 267, creatinine 4.9 mg/dL and creatinine clearance was 13 mL/min/1.73 m^2 (renal Failure according to RİFLE criteria). ACEİ and ARB treatments stopped and verapamil started. Her abdominal angiography revealed 70% stenosis at superior mesenteric artery and long segment stenosis at both renal artery proximal (Figure 1). Technetium-99m-labeled dimercaptosuccinic acid (DMSA) scans left kidney is bigger than right kidney and the differential functioning of the left is 90% and right 10%.

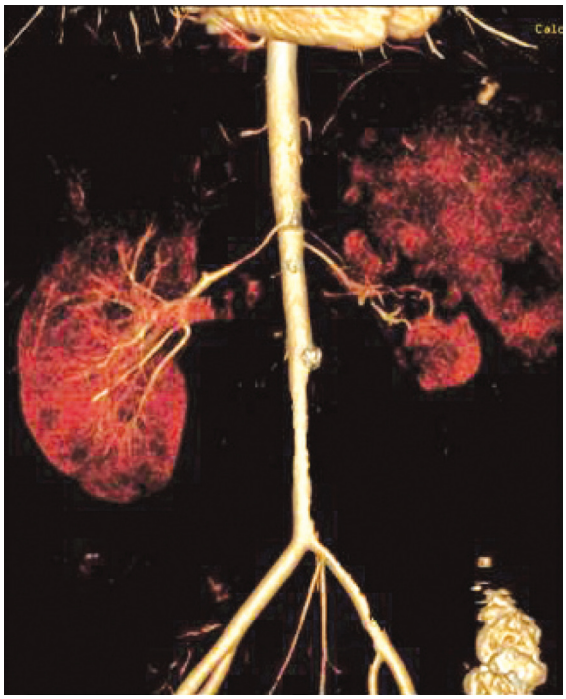

Figure 1. Long segment stenosis of right main renal artery at 3D computerized tomography

Discussion

Renovascular disease causes 5–10% of all childhood hypertension [9]. RAS (Renal artery stenosis) is the third most common pathological condition giving rise to a significantly sustained hypertension in children. The pathophysiology of hypertension caused by RAS is based on a decrease in the renal perfusion, which will activate the renin-angiotensin system to result in sodium and water retention as well as peripheral vessel constriction, finally culminating in hypertension.

Various diseases are associated with childhood renovascular hypertension. Several rare syndromes are associated with childhood renovascular hypertension [10]. The most common one is neurofibromatosis type 1. The frequency of the association between renovascular hypertension and neurofibromatosis type 1 is reported very differently, with a range of 7–58% [11]. Our two cases presented with neurofibromatosis and systemic arterial hypertension had stenotic lesions of renal arteries evaluated as midaortic syndrome (MAS). Neurocutaneous syndromes are the cause of MAS in 5% cases [12]. The location of lesion in MAS is inter-renal in 19–52% of cases, supra-renal in 11–40%, infra-renal in 19–25% and diffuse in 12% [13]. The renal arteries were involved in 91% of cases, of which 67% were bilaterally affected.

Indications for surgery are uncontrolled hypertension, kidney survival at risk (in cases with a very stenotic renal artery, surgery may be indicated to avoid loss by thrombosis when the blood pressure is lowered), claudication and intestinal ischemia.

Surgical correction of idiopathic MAS remains the definitive treatment when technically feasible. However, with effective anti-hypertensive treatment, conservative therapy is often possible prior to surgery. In cases where the level of operative risk is deemed unacceptable or in the very young medical treatment is sometimes the only option.

Hypertension is typically severe and often difficult to manage, and it requires treatment with a combination of multiple classes of medications. The choice of anti-hypertensive medications is similar to other forms of renovascular hypertension. Careful use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, necessitating monitoring of serum potassium and creatinine concentrations, is essential. Patients should be followed regularly for blood pressure control, renal function and growth of kidneys. Risks of hypertension, vascular flow compromise and side effects of medications need to be weighed against the surgical options when medical treatment is employed. Conservative therapy should not be pursued at the expense of renal or other organ impairment. Treatment with a multi-drug regimen may not be optimal, but our experience shows that it can be achieved, especially in cases in which surgical correction is not an option.

Although NF1 is a rare disease, it is an important cause of renovascular hypertension in childhood. Abdominal bruit is an alerting physical finding in diagnosis of renal artery stenosis. Our cases emphasize the need for blood pressure measurement in children with NF1. Screening for stenosis in the major branch vessels of the aorta in children with NF1 and renal artery stenosis is required in hypertensive NF1 patients.

Conflict of interest: The authors declared no conflict of interest.

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