

Increased arterial stiffness causing resistant hypertension in an adolescent with Neurofibromatosis type 1

Min Jung Cho

Department of Pediatrics, Pusan National University Hospital, Busan, Korea

Neurofibromatosis type 1 is an autosomal dominant genetic disorder characterized by the presence of café au lait spots, axillary and inguinal freckling, Lisch nodules, and neurofibromas. Hypertension is a relatively frequent complication, usually caused by renal artery stenosis or pheochromocytomas. We describe the case of a 15-year-old boy with neurofibromatosis type 1 who was also diagnosed with resistant hypertension. Despite an extensive evaluation, the etiology of his hypertension remained indeterminate. Estimation of the brachial-ankle pulse wave velocity and ambulatory arterial stiffness index could validate the existence of arterial stiffness. Further, a combination of carvedilol and angiotension receptor blockers was administered, which successfully controlled his resistant hypertension. We propose that the estimation of the brachial-ankle pulse wave velocity measure and ambulatory arterial stiffness index is a noninvasive method, and these two parameters are relatively simple tools that can be used for the detection of arterial stiffness due to neurofibromatosis type 1-related vasculopathy.

Key Words: Arterial stiffness, Hypertension, Neurofibromatosis type 1, Vasculopathy

Neurofibromatosis type 1 (NF1) is a well-known autosomal dominant genetic disorder with an incidence and a prevalence of approximately 1 in 3,500 and 1 in 4,500, respectively, in newborns.¹ Hypertension is a relatively frequent (2%~15.8%) complication in patients diagnosed with NF1.² Differential diagnosis of hypertension in patients diagnosed with NF1 includes renal artery stenosis and pheochromocytoma, among others. However, it is assumed that the incidence of these two conditions in NF1 patients is only 3%² and 3%~5%,³ respectively, which suggests some other underlying pathology to explain

hypertension occurring in patients with NF1. Arterial stiffness in association with NF1-induced vasculopathy^{2,4} or increased catecholamine production by the numerous neurofibromas⁵ observed in this disorder has been proposed as possible mechanisms causing hypertension, although the precise mechanisms remain unknown. We present an interesting case of resistant hypertension in a young boy, as a result of arterial stiffness noted in association with NF1 vasculopathy.

Corresponding Author: Min Jung Cho, Department of Pediatrics, Pusan National University Hospital, 179, Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7800 Fax: +82-51-248-6205 E-mail: mjchomd@gmail.com

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CASE

A 15-year-old boy with a known diagnosis of NF1 was admitted to our pediatric department due to resistant hypertension over 4 months. Hypertension was incidentally discovered at the time of the preoperative evaluation for an orthopedic surgery. Despite extensive investigations to detect secondary causes of hypertension, including renal artery stenosis, pheochromocytoma, aortic coarctation, hyperthyroidism, and primary aldosteronism, the etiology of his hypertension remained indeterminate. Moreover, despite being administered three antihypertensive medications, his blood pressure was poorly controlled over the following 4 months.

Upon admission, his blood pressure measured 180/90 mmHg without significant discrepancy in all four extremities. His heart rate was 84 beats per minute and his respiratory rate was 20 breaths per minute. He showed a persistently marked elevation of blood pressure ranging between 140/85 mmHg and 210/120 mmHg. He complained of an occasional headache but denied blurry vision or other neurological deficits. He was 164 cm tall (22nd percentile), weighed 47 kg (14th percentile), and his body mass index was 17.5 kg/m² (14th percentile). A physical examination revealed multiple café au lait spots on his trunk, axillary freckling, and several Lisch nodules on the surface of both irises. Funduscopic examination, chest X-ray, electrocardiogram, and echocardiography results were unremarkable. Brain magnetic resonance

imaging showed high signal intensity lesions in the thalamus, right basal ganglia, and periaqueductal area of his midbrain, but there was no hypothalamic lesion or vascular malformation. A urinalysis including urine microalbumin was normal. A laboratory evaluation revealed a normal complete blood count and the following levels: serum creatinine 0.57 mg/dL, blood urea nitrogen 12.5 mg/dL, sodium 139.7 mEq/L, potassium 3.17 mEq/L, and chloride 96 mEq/L. His thyroid-stimulating hormone, thyroxine, and cortisol levels were normal. Plasma catecholamine levels were all normal, indicating his epinephrine was 54.8 pg/mL (reference range if sitting, < 60), norepinephrine was 294.3 pg/mL (reference range if sitting, < 750), and dopamine was 11.9 pg/mL (< 87). His 24-hour urinary catecholamine excretion was also normal. Plasma renin and aldosterone were slightly increased showing plasma renin 6.93 ng/mL/hr (reference range 1.31~3.95 ng/mL/hr), and plasma aldosterone 1155.31 pg/mL (reference range 35~300 pg/mL). Renal Doppler ultrasound and computed tomography angiogram of the abdomen did not show renal artery stenosis. However, a renal angiography and bilateral renal venous catheterization were performed for confirmation, and no definite lateralization of plasma renin activity was observed (left side 29.22 ng/mL/h, right side 26.94 ng/mL/h). Moreover, no stenotic lesion was found. A computed tomography angiogram of the aorta confirmed no vascular deformities, such as stenosis and/or occlusion of the entire aorta.

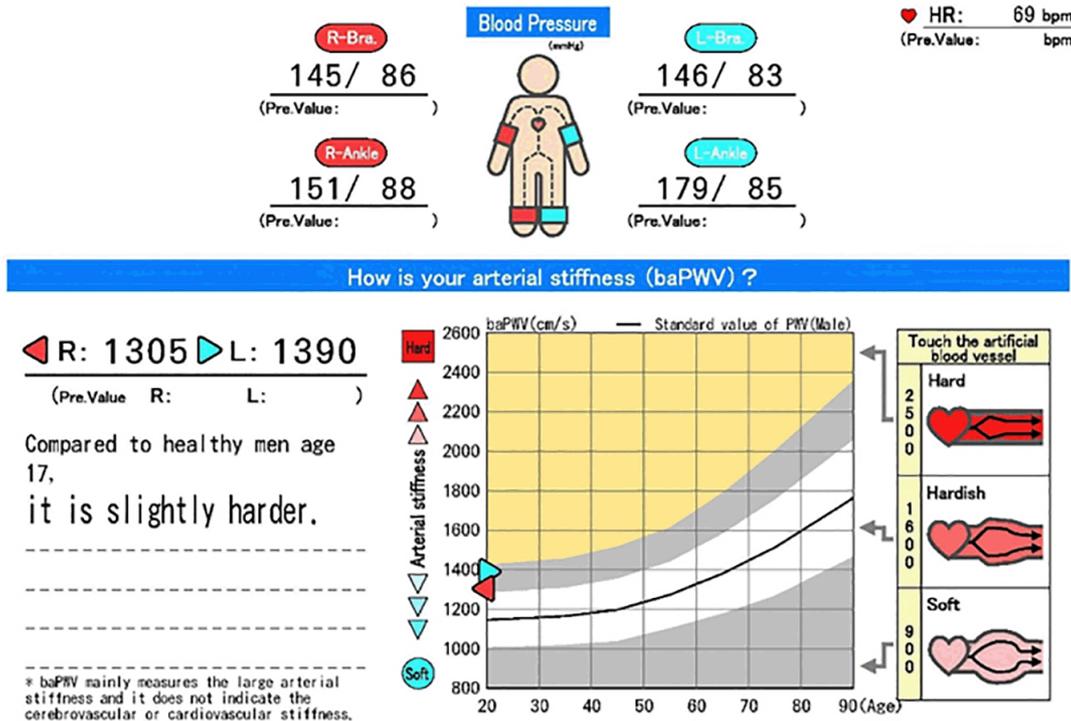


Fig. 1. Brachial-ankle pulse wave velocities. Markedly elevated for his age; 1305 cm/s for right and 1390 cm/s for left

We evaluated the patient’s brachial-ankle pulse wave velocity and the ambulatory arterial stiffness index on the basis of a 24-hour ambulatory blood pressure to confirm whether the arterial stiffness was a cause of his resistant hypertension. The brachial-ankle pulse wave velocity was markedly elevated for his age, 1305 cm/s on the right and 1390 cm/s on the left (Fig. 1). Additionally, ambulatory arterial stiffness index, which can be calculated as one minus the slope of the regression line, computed through all points given by the diastolic on systolic values of a single 24-hour recording, was elevated to 0.601 (reference range 0.35 ± 0.18).

Treatment with intravenous labetalol (a combination of alpha- and beta-adrenergic blockers) was initiated at a dose of 0.3 mg/kg/h. As his blood

pressure began to stabilize with the use of intravenous labetalol, he was gradually switched to the use of oral carvedilol and losartan. At the time of discharge, his blood pressure was 130/80 mmHg. Upon the patient’s discharge, he was prescribed a regimen of oral carvedilol at a 25 mg dose every 12 hours and losartan at a 50 mg dose every 24 hours.

DISCUSSION

To the best of our knowledge, this is the first report that proves the presence of arterial stiffness contributing to resistant hypertension in an adolescent with NF1 using noninvasive parameters,

such as estimation of the brachial-ankle pulse wave velocity and ambulatory arterial stiffness index. Furthermore, this case proves that arterial stiffness by itself can cause resistant hypertension in the absence of renal artery stenosis or pheochromocytoma in patients with NF1.

Previous studies have described that hypertension is detected in approximately 2%~15.8% of children diagnosed with NF1.^{2,4} Although both renal artery stenosis and pheochromocytoma are major causes of hypertension in patients diagnosed with NF1, some patients with NF1 show increased blood pressure based on 24-hour ambulatory blood pressure recordings without an identifiable cause to explain the hypertension.⁴ Several hypotheses have been suggested to account for the cause of increased blood pressure in patient cases with NF1. Increased catecholamine production by neurofibromas has been proposed as one of the mechanisms causing increased blood pressure in patients with NF1.⁵ However, in our case, there was no evidence to support the role of catecholamines, as the patient showed normal catecholamine levels. Arterial stiffness is a widely accepted hypothesis to explain the cause of increased blood pressure noted in NF1 patients. Despite extensive evaluation, the etiology of drug-resistant hypertension remained indeterminate in our young and thin patient with NF1. Therefore, we evaluated the brachial-ankle pulse wave velocity and ambulatory arterial stiffness index in an attempt to prove the existence of arterial stiffness as a causative factor for hypertension in this case. Notably, this

is the first case which proves the causative role of arterial stiffness in drug-resistant hypertension in a patient with NF1 using the brachial-ankle pulse wave velocity and ambulatory arterial stiffness index as useful clinical assessment parameters.

Presently, estimation of the brachial-ankle pulse wave velocity is the most effective method for the direct measurement of arterial wall stiffness in children.⁶ It is easily calculated by measuring the velocity of the pulse wave that travels a given distance between two sites along the arterial system.⁷ Additionally, the ambulatory arterial stiffness index is a newer indirect parameter for evaluating arterial stiffness. The index is calculated based on a 24-hour ambulatory blood pressure recording using the formula: 1 minus the slope of the regression of the 24-hour systolic blood pressure readings on the diastolic blood pressure readings. Previous studies report that the ambulatory arterial stiffness index is elevated in children and young adults with primary hypertension and secondary to repaired coarctation of the aorta.⁸

Previous studies have also shown that most hypertensive patients with NF1 tend to be asymptomatic except in cases where their hypertension is related to renal artery stenosis or pheochromocytoma. In such cases, the patients show a mild degree of hypertension detected solely by a 24-hour ambulatory blood pressure recording.^{2,4} Clinical manifestations in this case (resistant hypertension in a young and thin patient) were somewhat different from the usual results seen in cases of primary hypertension with no identifi-

able cause of the elevated blood pressure. Another interesting feature validated by this case is the fact that such resistant hypertension could be precipitated merely by arterial stiffness in patients with NF1.

Based on the increase in arterial stiffness, we finally opted for treatment with carvedilol, which is a non-cardio-selective beta blocker having vasodilating properties ascribed by alpha 1-adrenergic blocking effect, in combination with an angiotensin receptor blocker as angiotensin receptor blockers are considered superior to other anti-hypertensives in alleviating arterial stiffness.⁹ Use of this medication regimen could successfully control our young patient's resistant hypertension.

In conclusion, this case report proposed that resistant hypertension can be precipitated by the arterial stiffness itself in patients with NF1. Using the brachial-ankle pulse wave velocity and ambulatory arterial stiffness index, we could prove the role of arterial stiffness as a causative factor for resistant hypertension in a patient diagnosed with NF1. The brachial-ankle pulse wave velocity and ambulatory arterial stiffness index are noninvasive and relatively simple tools which can be used for the detection of arterial stiffness arising from NF1-related vasculopathy.

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