

# Systemic hypertension followed by insidious stroke in a 12-year-old boy with childhood neurofibromatosis type 1 presenting with renal and cerebral artery vasculopathy

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**SUMMARY:** Lee ML, Chang TM, Yang RC, Yang AD, Chen M. Systemic hypertension followed by insidious stroke in a 12-year-old boy with childhood neurofibromatosis type 1 presenting with renal and cerebral artery vasculopathy. Turk J Pediatr 2019; 61: 629-634.

Neurofibromatosis type 1 (NF1)-associated vasculopathy is usually diagnosed decades after the clinical diagnosis of NF1. Childhood NF1-associated renal artery vasculopathy or moyamoya-like brain vasculopathy could be clinically silent for a long time. We report a 12-year-old boy who had systemic hypertension found incidentally at a routine check-up. Physical examination showed café-au-lait spots and strong radial pulses. Abdominal computerized tomography angiography showed severe right ostial renal artery stenosis. Genomic study showed a heterozygous mutation c.5902C>T (p.R1968\*) and two heterozygous single nucleotide polymorphisms (NCBI: SNP rs18011052 and rs2905876) of *NF1* gene. After endovascular revascularization for renovascular hypertension caused by renal artery stenosis, including percutaneous transluminal renal angioplasty and stent implantation, blood pressure dropped effectively from 205/143 mmHg to 130/90 mmHg. Supine renin level dropped from 87.2 pg/mL to 47.9 pg/mL. Unfortunately, right hemiplegia, transient visual loss with blind spots (scotomas), and clumsiness of extremities emerged insidiously 3.5 months later. Brain magnetic resonance imaging and magnetic resonance angiography showed ischemic infarction involving the watershed area of the anterior and middle cerebral arteries, indicating presence of moyamoya-like brain vasculopathy. A dilemma is that a significant decrease of blood pressure after endovascular revascularization for renal artery stenosis may have potentially unmask the moyamoya-like brain vasculopathy in this patient. Vasculopathy could be heralding childhood NF1 in the young patients without full-fledged clinical features. Endovascular revascularization for renal artery stenosis could be a double-edge sword in childhood NF1 presenting with concomitant renal and cerebral artery vasculopathy.

**Key words:** neurofibromatosis type 1, vasculopathy, percutaneous transluminal renal angioplasty, stent implantation, moyamoya syndrome.

Neurofibromatosis type 1 (NF1; OMIM #162200) is an inherited multisystem disorder caused by dominant loss-of-function mutations of the tumor-suppressor gene *neurofibromin 1* (*NF1*; OMIM #613113) which is located at 17q11.2.<sup>1</sup> A diagnosis of NF1 can be made if two of the following criteria are met, including café-au-lait spots,

intertriginous freckling, dermal neurofibroma, optic glioma, Lisch nodules, skeletal dysplasia, and a positive family history.<sup>2</sup> We report a case who presented clinically with silent renal and cerebral arterial vasculopathy, illustrating the caveats in the diagnosis and management of childhood NF1.

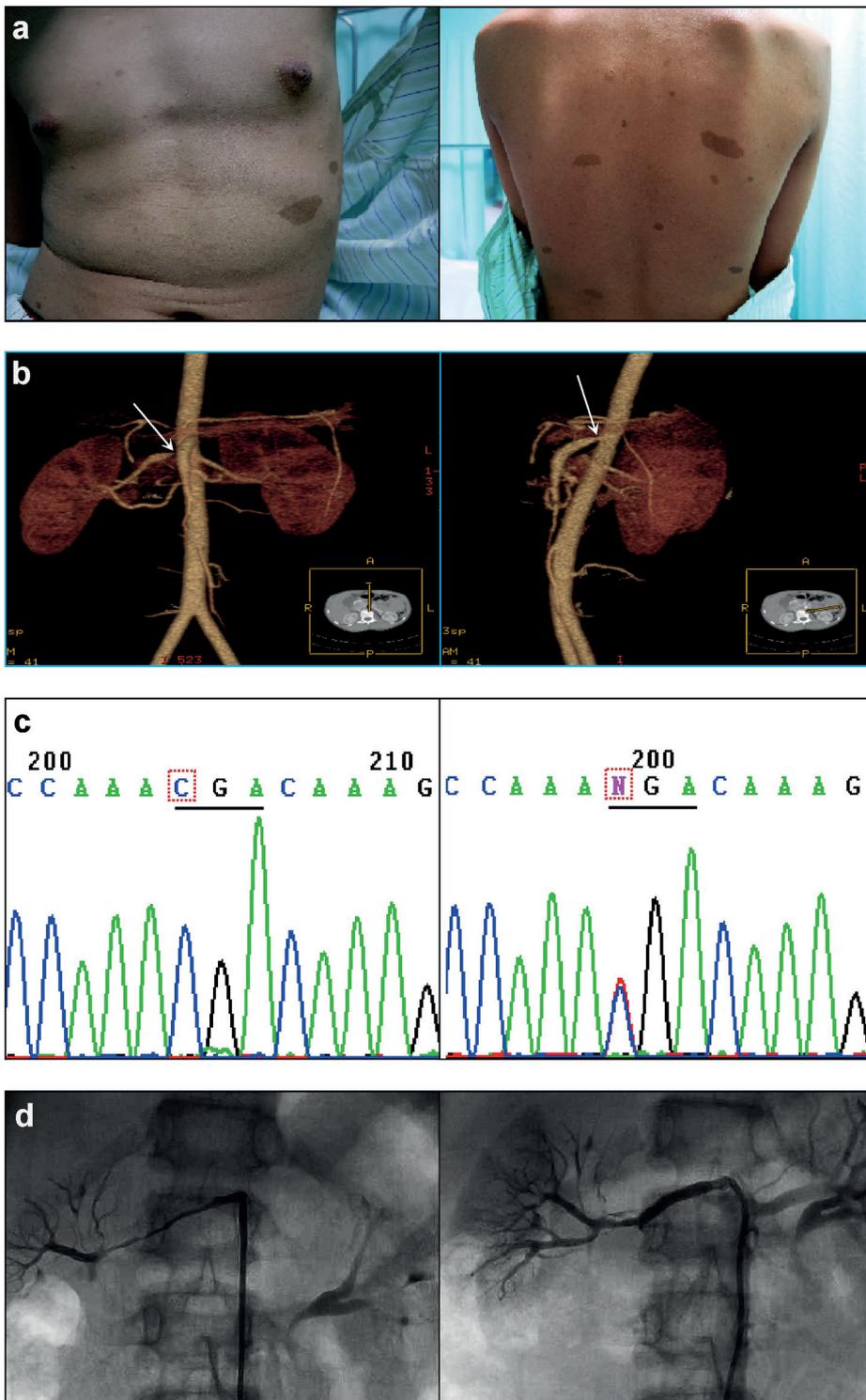
## Case Report

A 12-year-old boy was referred to our tertiary medical center with a chief complaint of systemic hypertension (190/98 mmHg) found incidentally at a routine check-up of blood pressure at a local clinic. At referral, he remained asymptomatic. Café-au-lait spots were discernible (Fig. 1a). Under the presumed diagnosis of NF1, abdominal computerized tomography angiography was performed and established a severe right ostial renal artery stenosis (RAS) (Fig. 1b, left panel), total occlusion of the celiac trunk, and moderate stenosis of the superior mesenteric artery (SMA) (Fig. 1b, right panel). On admission, he weighed 46 kg and 156 cm in height. Blood pressure was 190/98 mmHg, heart rate 108/min, and respiratory rate 22/min. Bilateral radial/femoral pulses were bounding. There were no abdominal and carotid bruits. Electrocardiogram showed left ventricular hypertrophy by voltage. Erythrocyte sedimentation rate was 11 mm/hr. Genomic study showed a heterozygous mutation c.5902C>T (p.R19689\*) and two heterozygous single nucleotide polymorphisms (NCBI: SNP rs18011052 and rs2905876) of *NF1* gene (Fig. 1c). By cardiac catheterization, aortic pressure was 205/143 mmHg. Angiography of the right renal artery confirmed ostial RAS (2.24 mm; stenosis ratio of 59%). Percutaneous transluminal renal angioplasty (PTRA) was performed after informed consent from his parents. We used a coronary balloon catheter of 4.5 mm x 15 mm (Sprinter Legend, Medtronic, Galway, Ireland) to perform PTRA, with a distended pressure increased gradually from 6 atm to 14 atm (a maximum diameter of 4.55 mm). Stenosis ratio improved from 59% to 10%. Supine renin level dropped from 29.2 pg/mL to 20.4 pg/mL (normal range: <3.6-20.1 pg/mL). However, blood pressure fluctuated around 150-170/90-110 mmHg in the following three weeks. Supine renin level increased from 20.4 pg/mL to 87.2 pg/mL. Under the impression of restenosis of the right renal artery, he was admitted for repeated PTRA. Aortic pressure was 183/106 mmHg on cardiac catheterization. Angiography showed a long-segment right RAS (0.42 mm; stenosis ratio of 87%) (Fig. 1d, left panel). At first, we used two sets of coronary

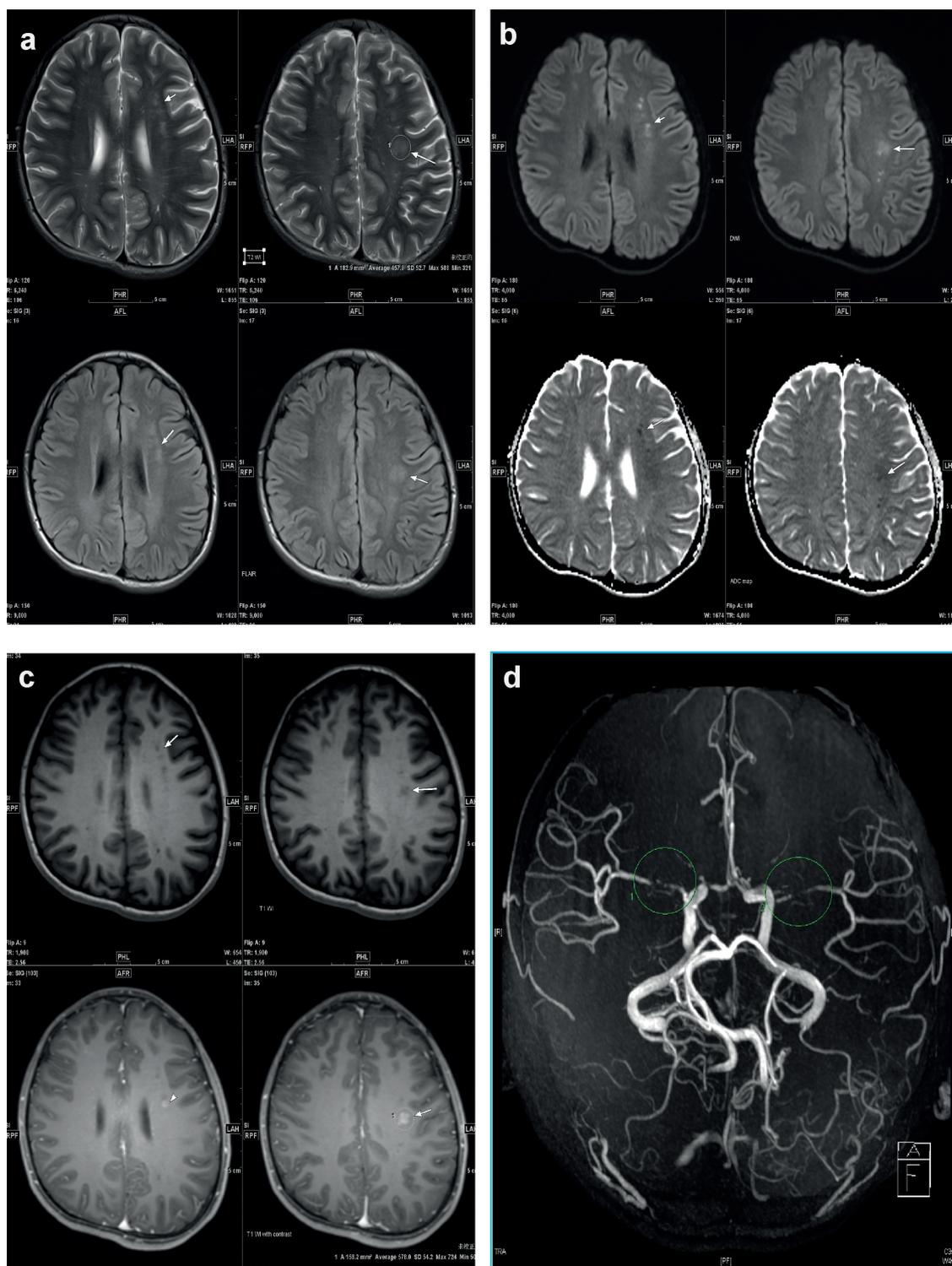
balloon catheter (3.5 mm x 20 mm, Sprinter Legend, Medtronic, Galway, Ireland; 5.00 mm x 12 mm, NC TREK, Abbott Vascular, Diegem, Belgium) to dilate this long-segment right RAS stepwise from the main trunk to the ostium of the right renal artery, with no success. Afterward, we used a longer coronary balloon catheter (3.5 mm x 30 mm, Sprinter Legend, Medtronic, Galway, Ireland) to perform high-pressure PTRA, with a distended pressure maintained at 14 atm and for 2 minutes. However, the restenosis remained refractory to high-pressure PTRA. A stent was implanted to prevent total occlusion of the right renal artery (4.0 mm x 38 mm, Abbott Coronary Stent, Abbott Vascular, Diegem, Belgium). Post-intervention angiography showed patent flow from the abdominal aorta through the right renal artery to the right kidney (Fig. 1d, right panel). Blood pressure dropped from 183/106 mmHg to 130/90 mmHg. Supine renin level dropped from 87.2 pg/mL to 47.9 pg/mL. Aspirin was prescribed for anticoagulation. Clinical symptoms and signs of transient ischemic attack (TIA), including right hemiplegia, transient visual loss with blind spots (scotomas), and clumsiness of extremities, emerged insidiously 3.5 months after the intervention. Brain magnetic resonance imaging (MRI) showed ischemic infarction involving the deep watershed zone of the anterior and middle cerebral arteries, including T2-weighted and fluid-attenuated inversion recovery images (Fig. 2a), diffusion weighted imaging with apparent diffusion coefficient (Fig. 2b), and T1-weighted images with gadolinium enhancement (Fig. 2c). Brain magnetic resonance angiography (MRA) showed stenoses of intracranial carotid arteries and bilateral middle cerebral arteries (Fig. 2d), indicating moyamoya syndrome (MMS) associated with NF1. His intelligence quotient score was 71 (normal range: 90-110), which was assessed by the Wechsler Intelligence Scale for Children. He was later lost in the follow-up.

## Discussion

This case carries five points to be highlighted. First, the patient presented with only one criterion of NF1, namely, cutaneous café-au-lait spots. However, genomic study showed a



**Fig. 1.** (a) Café-au-lait spots were noted over abdomen (left panel) and back trunk (right panel). (b) Abdominal computerized tomography angiography showed severe right ostial renal artery stenosis (left panel) and stenosis of the superior mesenteric artery (right panel). (c) Genomic study showed a heterozygous mutation c.5902C>T (p.R1968\*) and two heterozygous single nucleotide polymorphisms (NCBI: SNP rs18011052 and rs2905876) of the *NF1* gene. (d) Right renal arteriography showed a long-segment restenosis of the right renal artery after percutaneous transluminal renal angioplasty (left panel), and patent blood flow through the right renal artery after stent implantation (right panel).



**Fig. 2.** Brain magnetic resonance imaging showed ischemic infarction involving the watershed zone of the anterior and middle cerebral arteries (arrows), including (a) T2-weighted images (upper two panels) and fluid-attenuated inversion recovery (FLAIR) images (lower two panels), (b) diffusion weighted imaging (DWI; upper two panels) and apparent diffusion coefficient (ADC; lower two panels) mapping, and (c) T1-weighted images without gadolinium contrast enhancement (upper two panels), and T1-weighted images with gadolinium contrast enhancement (lower two panels). (d) Brain magnetic resonance angiography showed stenoses involving bilateral middle cerebral arteries (circles).

heterozygous mutation c.5902C>T (p.R1968\*) and two heterozygous single nucleotide polymorphisms (NCBI: SNP rs18011052 and rs2905876) in the *NF1* gene. DeBella et al.<sup>2</sup> reported that approximately 46% of sporadic cases fail to meet the NIH Diagnostic Criteria by 1 year of age whereas 97% meet the criteria by 8 years old, and all do so by 20 years old, and they proposed that a modification of the diagnostic criteria for NF1 in children. Given that *NF1* mutation could be detected in 97% of 565 patients with NF1,<sup>1</sup> *NF1* mutation analysis may be suggested in young children without full-fledged features of NF1.

Second, NF1 vasculopathy was coined to describe a pleiotropic array of vascular abnormalities identified in patients with NF1.<sup>3</sup> In four large series of childhood NF1, the prevalence of cerebral artery vasculopathy was 2.5%-6.4%, and that of MMS was 0.6%-4.9%.<sup>4-7</sup> Considering relatively low incidence of cerebral artery vasculopathy and MMS in childhood NF1, clinical guidelines did not advocate neuroimaging in the asymptomatic patients as routine examinations.<sup>8</sup> Oderich et al.<sup>9</sup> reported that the incidence of vasculopathy of renal artery, carotid-vertebral-cerebral artery, and aorta were 41%, 19%, and 12%, respectively. In this regard, routine check-up of blood pressure is warranted in patients with suspected NF1, and systemic hypertension can be served as a harbinger of NF1 that is most liable to incur renal artery vasculopathy in terms of RAS. Overall, a diagnosis of NF1 and NF1 vasculopathy was made at  $11 \pm 10$  years and  $38 \pm 16$  years, respectively,<sup>9</sup> which implies that vasculopathy emerged after a lapse of two to three decades and the incidence of vasculopathy will increase with time. Thus, vasculopathy is a hallmark not only heralding childhood NF1 in the young population without full-fledged features, but also implicating excess deaths in patients <30 years of age.<sup>10</sup> It is foresighted to include vasculopathy as a diagnostic clue to facilitate an early diagnosis of childhood NF1, especially in those cases presenting with renovascular hypertension, TIA or stroke (cerebral artery vasculopathy), differential hypertension of the upper limbs (thoracic aorta vasculopathy), intestinal gangrene (SMA or celiac trunk vasculopathy), and disabling claudication

(aorto-iliac artery vasculopathy).

Third, a thorough understanding of the pathogenesis of NF1 vasculopathy may clarify its progressive or relapsing nature. NF1 vasculopathy is assumed to be a developmental lesion, with a genetic predisposition to progression.<sup>11</sup> It is given that neurofibromin, encoded by the *NF1* gene, serves as a GTPase activating protein that accelerates conversion of active *Ras*-GTP to inactive *Ras*-GDP.<sup>11</sup> The mutation of the *NF1* gene results in loss of neurofibromin expression in the endothelial cells, accumulation of *Ras*-GTP, and a perturbation of vasculogenesis.<sup>11</sup> Intriguingly, the alteration of the morphogenic phenotype of NF1 vasculopathy appears to be quite plastic, for the acquisition of an additional mutation or epigenetic silencing of the remaining copy of *NF1* gene may trigger *Ras* activation and render autonomous proliferation and abnormal formation in the post-developmental quiescent vasculature.<sup>11</sup> That is why NF1 vasculopathy may display a plethora of morphology, including aneurysm, stenosis, arteriovenous malformation, and moyamoya.<sup>9,11</sup>

Fourth, antihypertensive agents were usually palliative, but not curative, for renovascular hypertension due to RAS in childhood NF1. Because of the progressive nature of childhood RAS, repeated PTRAs have been advocated as an initial treatment of choice, disregarding its underlying disease.<sup>12</sup> Stent implantation should be reserved as a bailout procedure for childhood RAS, if results are suboptimal or dissection occurs after PTRAs.<sup>13</sup>

Finally, moyamoya disease is referred to the occlusion of bilateral arteries of the circle of Willis of unknown origin, and MMS is defined as an underlying disease having similar pathognomonic arteriographic finding of a puff of smoke (moyamoya). Surgical revascularization is safe and effective in preventing further ischemic and neurological damage in children with NF1-associated MMS.<sup>14</sup> However, it can be a double-edge sword for childhood MMS because it may also cause postoperative neurological deterioration due to cerebral ischemia (watershed shift) or cerebral hyperperfusion syndrome.<sup>15</sup> A significant decrease of blood pressure by

intervention may lead to ischemic infarction by a vascular steal phenomenon of the watershed zones and cause TIA or cerebrovascular stroke in the present patient.

In conclusion, renal and cerebral vasculopathy in NF1 can be silent for a long time. The pediatrician's role is crucial for a timely diagnosis of these complicated but treatable conditions, as measurement of the blood pressure and examination of the skin during routine pediatric visits provide the diagnostic clues.

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