Renovascular hypertension due to bilateral renal artery stenosis treated with stent implantation in a 12-year old girl

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Renovascular hypertension (RVH) in children is a relatively rare disease, but it is important in that it is a treatable condition when properly diagnosed. Percutaneous transluminal renal angioplasty (PTRA) with or without stenting is widely applied to adult patients with RVH. However, limited information is available as to PTRA with stenting in pediatric patients. We experienced a case of RVH in a 12-year-old girl, who had severe hypertension (180/110 mmHg). Bilateral renal artery stenosis was demonstrated by 3D-CT, MR angiography and selective renal arteriography. Renal function and plasma renin activity were normal. Angiotensin blockade was refrained for fear of functional deterioration of the kidney. Medical treatment with amlodipine insufficiently lowered the pressure to 140-160/80-100 mmHg, so we performed PTRA. Stenotic lesion and pressure gradient was still present after balloon angioplasty on both sides, prompting us to place LUMINEXX stents on both renal arteries. Blood pressure dropped dramatically after the intervention. Amlodipine was discontinued, and then, enalapril and warfarin were administered to prevent neo-intima and thrombus formation. Her blood pressure and renal function was stable 18 months after PTRA. Oversized self-expanding stent such as LUMINEXX[®] stent could be used for renal artery stenting even in pediatric patients with RVH.

Key words: Renovascular hypertension, PTRA, Stent, Pediatrics, Interventional radiology

INTRODUCTION

Renovascular hypertension (RVH) is one of the most important causes of hypertension in children, although its incidence is not so frequent. In adults, atherosclerosis of renal artery is the most important etiology of RVH, whereas fibromuscular dysplasia is of greater importance in children [1, 2]. It is now recognized that not only Takayasu's arteritis but also antiphospholipid antibody syndrome with or without systemic lupus erythematosus can cause RVH, especially in young females [3-14]. As to the treatment of RVH, in addition to medical management with antihypertensive agents, interventional approaches such as balloon angioplasty and, more recently, stent placement has provided us with new treatment modality which is now widely applied to the adult patients with RVH [15-24]. However, stent placement in pediatric RVH patients has not yet gained general consensus [25-30]. Further, long-term feasibility of stent placement even in adult RVH patients is still controversial [31]. We report here a 12-year-old girl with renovascular hypertension due to bilateral renal artery stenosis, which was treated by percutaneous transluminal renal angioplasty (PTRA) with stent implantation.

CASE REPORT

A 12-year-old girl was referred to our hospital because of severe hypertension. Two months prior to her visit to our hospital, she noted that her blood pressure was elevated as high as 180/110 mmHg at home "by chance" when she measured her blood pressure with her grandmother who had been under medication for hypertension. At that time, she had no hypertensionrelated symptoms including headache and chest pain. She saw a local medical doctor and then she was referred to Isehara Kyodo Hospital because of remarkable hypertension. Physical and laboratory examination revealed uniformly elevated blood pressure on all the four limbs, and normal renal function. Although plasma renin activity was not elevated, imaging analyses such as Doppler ultrasonography and MR angiography were suggestive of bilateral renal artery stenosis. So, she was referred to Tokai University Hospital for further evaluation and possible intervention aiming at revascularization.

Family history revealed hypertension in her grandmother who provided our patient with an opportunity to measure blood pressure at home. Past history was unremarkable. She had no episode of persistent fever with unknown origin, and no symptoms such as stomatitis, arthritis and skin rash, which suggest autoimmune disease.

Physical examination revealed a conscious, active and well-nourished girl, with the height of 158.4 cm (+1.2 SD) and the weight of 45.6 kg (+0.2 SD). Blood pressure was 176/106 mmHg on her right arm. No remarkable difference in blood pressure was noted on the extremities. Peripheral arteries were well pulsated on all four limbs. Vascular bruit was not remark-

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Table.	Summary	of	laboratory	y find	ings
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Table. Summary of Taboratory Tindings						
Hematology	Immunology					
WBC 4350 / $\mu \ell$ RBC 440 / $\mu \ell$ Hb 12.5 g/d ℓ Plt 20.3x10 ⁴ / $\mu \ell$	ANA C3 C4 anti dsDNA Ab anti Cardiolipin Ab Lupus anticoagulant	negative 86 mg/dl 10 mg/dl 25.3 IU/ml 23 U/ml negative				
$\begin{tabular}{c c c c c c } \hline Clinical Chemistry \\ \hline TP & 6.9 & g/d\ell \\ \hline Alb & 44 & g/d\ell \\ \hline BUN & 14 & mg/d\ell \\ \hline Cr & 0.6 & mg/d\ell \\ \hline Na & 141 & mEq/\ell \\ \hline \end{tabular}$	Others fT4 TSH PRA Aldosterone	0.93 ng/dl 1.20 μU/ml 2.3 ng/ml/hr 100 pg/ml				
K 44 mEq/ ℓ Cl 105 mEq/ ℓ	Ang II <u>renal vein sampling</u> (pla	5 pg∕mℓ sma renin activity)				
LDH 377 U/l CRP <0.09 mg/dl Coagulation	left renal vein right renal vein inferior vena cava	1.8 ng/ml /hr 1.7 ng/ml /hr 1.9 ng/ml /hr				
PT 14.3 sec	Captopril loading test (p					
$\begin{array}{llllllllllllllllllllllllllllllllllll$	pre : post :	4.1 ng/ml /hr 13.0 ng/ml /hr				

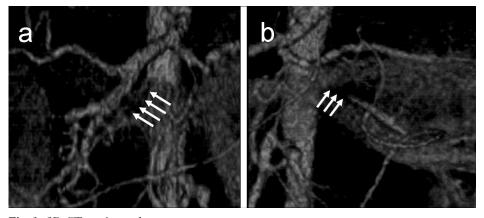


Fig. 1. 3D-CT angiography Arrows indicate the stenotic segments of right (a) and left (b) renal arteries.

able even on careful auscultation of upper abdomen. Funduscopic findings were negative for hypertensive changes.

Laboratory findings are summarized in Table. Renal function was normal without electrolyte disturbances. D-dimer was not elevated, suggesting the absence of thrombus formation. Thyroid function was normal. Urinary excretion of catecholamine was not increased. Cushing syndrome was ruled out by the normal level of serum cortisol. Renin-angiotensin-aldosterone system did not seem to be activated. Although antinuclear antibody and anti-DNA antibody were negative, antidsDNA antibody was slightly elevated. Serum complements (C3 and C4) showed low-normal levels. Although lupus anticoagulant was negative, anti-cardiolipin antibody was slightly elevated. Because of the inconsistent serological findings and lack of specific clinical symptoms, we could not make diagnoses of a specific collagen disease nor antiphospholipid syndrome in this patient. She has not had any episode of persistent fever without remarkable focus, and any active inflammatory reaction is absent. So, the diagnosis of Takayasu's arteritis could not be confirmed, even though she had concomitant stenosis of superior mesenteric artery

as is mentioned later. Chromosomal FISH analysis for the Williams syndrome failed to demonstrate the deletion of the responsible genetic locus for Williams syndrome, which can be the cause of middle aortic syndrome [32]. Selective renal vein sampling revealed equivalent and normal plasma renin activity in both sides. Plasma renin activity significantly rose up from 4.1 ng/ml/hr to 13.0 ng/ml/hr, 1 hour after oral captopril administration of 37.5 mg. Renoscintigraphy recorded after captopril administration failed to show remarkable deterioration of renal function on both sides.

Imaging analyses including ultrasonography, 3D-CT, MR angiography and selective renal arteriography were performed. Right and left kidney sizes by ultrasonography were 8.6 cm (-2.0 SD for age) and 11.0 cm (+0.7 SD for age) in length, respectively. The main trunks of right and left renal arteries could hardly be demonstrated by ultrasonography and also by MR angiography (data not shown), suggesting that renal arteries were narrowed bilaterally at their main trunks. The renal arteries with stenosis were visualized by 3D-CT as shown in Fig. 1. The stenosis of the trunk of superior mesenteric artery (SMA) was also recognized

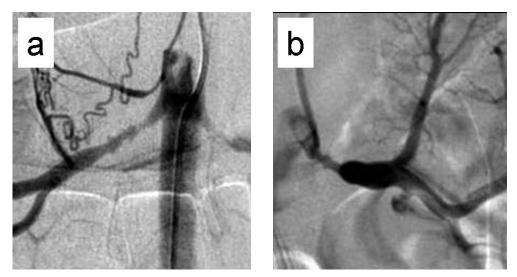


Fig. 2. Selective angiography of right (a) and left (b) renal arteries before PTRA.

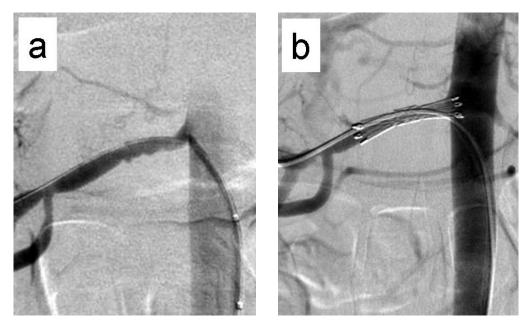


Fig. 3. Selective angiography of right renal artery after balloon angioplasty (a), and after additional stenting (b).

by ultrasonography and 3D-CT. Blood flow of SMA at the distal portion to the stenotic lesion was rather well preserved by collateral feeding arteries originating from celiac artery.

On the referral to our hospital, she was remarkably hypertensive (176/106 mmHg), prompting us to start antihypertensive treatment with amlodipine of 2.5 mg/ day. Amlodipine administration was effective in lowering her blood pressure to some extent, around 140 to 160 mmHg of systolic pressure, and 80 to 100 mmHg of diastolic pressure.

Interventional Radiology

Most of the laboratory findings were not suggestive of RVH, except for elevation of PRA after captopril administration. However, the imaging analyses were all compatible with RVH. Medical management with amlodipine administration was not satisfactory as mentioned above. She had bilateral renal artery stenosis, predisposing her at risk of angiotensin blockadeinduced renal dysfunction, so we hesitated to use angiotensin converting enzyme inhibitor or angiotensin receptor blocker for long-term medical management. Then, we performed selective renal arteriography, and bilateral renal arterial stenosis (Rt: 95%, Lt 90%) were clearly demonstrated as shown in Fig. 2. "String of beads" appearance suggested fibromuscular dysplasia. At the same time, PTRA was performed. First, balloon angioplasty was attempted on the right renal artery using Muso® balloon catheter at 10 atm. The stenotic waist of the right renal artery disappeared, leaving some irregularity of the arterial wall and pressure gradient of >50 mmHg between aorta and right renal artery (Fig 3a). So, a LUMINEXX® stent (Bard, U.S.A.), sized 6 x 20 mm, was implanted on the stenotic lesion of the right renal artery, resulting in disappearance of pressure gradient between aorta and the right renal artery (Fig 3b). Then, balloon angioplasty of the left renal artery was attempted at 12 atm, but the stenotic waist was left undilated (Fig 4a). So, we decided to

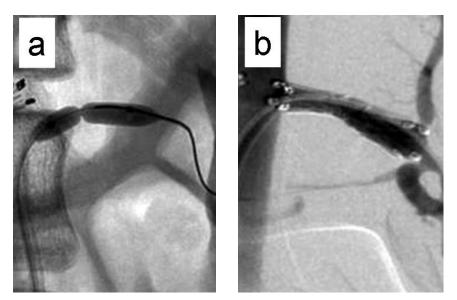


Fig. 4. Selective angiography of left renal artery during balloon angioplasty (a), and after additional stenting (b).

place a stent even on the left renal artery, using a LUMINEXX[®] stent of 6×20 mm in size (Fig 4b). Angiography of the celiac artery and supramesenteric artery (SMA) revealed remarkable stenosis of the trunk of SMA. At the same time, collateral perfusion via posterior superior pancreatoduodenal artery and postpancreatic arterial arcade was also visualized. Based on the presence of abundant collateral perfusion and the absence of clinical symptoms such as abdominal angina, we decided not to try revascularization of the SMA.

Clinical course after the intervention:

Blood pressure of the patient dropped dramatically to normal range after PTRA, around 110 to 120 mmHg of systolic pressure and 50 to 60 mmHg of diastolic pressure. Warfarin administration was started soon after the intervention to avoid thrombus formation on the stents. Enalapril of 2.5 mg was also started to avoid re-stenosis of the renal arteries and to control blood pressure. Amlodipine was discontinued 1 month after the intervention when we were assured that her blood pressure remained normal. Three months after the intervention, her systolic blood pressure became somewhat elevated to around 130 to 150 mmHg. Then, the dose of enalapril was doubled to 5 mg a day, resulting in stabilization of systolic blood pressure around 120 to 130 mmHg. Because of the artifact originating from the stents, evaluation of intra-stent and post-stent blood flow was difficult by Doppler ultrasonography, 3D-CT and MR angiography. Intrarenal perfusion, shown by Doppler ultrasonography, was well preserved on both kidneys 18 months after PTRA (data not shown).

DISCUSSION

Severe hypertension is a relatively rare condition in children compared to that in adults. The causes of hypertension are also different, i. e., secondary hypertension is predominant in children, whereas essential hypertension is much more common in adults. Renovascular hypertension is one of the most common and important cause of secondary hypertension in children [2]. Renovascular hypertension is important in that it is a curable condition when it is properly diagnosed. High plasma renin activity (PRA), elevation of PRA after oral administration of captopril and captopril-induced dysfunction shown by renoscintigraphy in the affected kidney have been proposed as useful diagnostic information for renovascular hypertension, especially in unilateral renal artery stenosis. In our patient, PRA was not elevated, and the both kidneys failed to show captopril-induced functional deterioration by renoscintigraphy, supposedly because of the "bilateral" stenosis of the renal artery [1]. So, imaging analyses were of great help to confirm the presence of renal artery stenosis in our patient. Among them, 3D-CT and selective renal arteriography were able to demonstrate the stenotic lesions. So, in this patient, 3D-CT is preferred to MRA as a less-invasive imaging analysis. Selective renal arteriography is still the gold standard to clearly demonstrate renal artery stenosis, as exemplified in our case.

Treatment of renovascular hypertension includes antihypertensive medicines, PTRA with or without stent implantation, and surgical repair. Surgical repair includes renal artery implantation to aorta or renal artery, aortorenal bypass with saphenous vein or iliac artery graft, and so forth [33]. Surgical repair has been shown to be safe and effective in pediatric patients with RVH, and has been preferably indicated in patients with an occluded or severe stenotic renal artery (>50%), Takayasu's arteritis, concomitant aortic or other arterial maldevelopment, and those in whom prior endovascular treatment had failed [30]. PTRA is apparently less invasive than open surgical repair. So, along with the recent advancement of interventional radiology, PTRA is now widely applied to patients with renovascular hypertension. Then, we chose PTRA as a first step to achieve revascularization in the patient presented. There is increasing information of the safety and efficacy even in the long term observation. Most of them were obtained from adult patients [15-24]. Long-term efficacy seems to be dependent on the nature of stenosis. RVH due to atherosclerosis often results in re-stenosis after PTRA even with stent implantation, and also experiences further deterioration of renal function, probably due to the concomitant presence of atherosclerotic lesion in the intrarenal vasculature. Rather favorable outcome after PTRA has been reported in patients with RVH due to fibromuscular dysplasia [34], encouraging us to expect a favorable prognosis in our patient who supposedly have fibromuscular dysplasia based on the "string of beads" findings in the arteriography. However, as to PTRA, especially with stent implantation, limited information is available in pediatric population [25-29]. In the recent report by Körnig et al [29], Palmaz[®] stent (4×11 mm) was implanted in a 6.5 year-old girl with fibromuscular dysplasia. In their case, the stent was successfully re-dilated 7 months after the initial intervention. In the case reported by Hirai et al [26], dislocation of the stent to the distal portion of renal artery took place, necessitating additional stent implantation. Clinical implication of PTRA with stent implantation is still controversial because of the lack of abundant experience in pediatric population. We cannot extrapolate from the adult patients-based information. Etiology of renal artery stenosis is different between adults and children, and the growth of the renal artery cannot be neglected in pediatric patients. In this milieu, re-dilatable stent such as Palmaz® stent, or oversized self-expanding stent such as LUMINEXX® stent might be the choice for pediatric patients. Körnig et al proposed that PTRA and stent implantation should be considered when medical treatment fails to control renovascular hypertension or renal function is decreasing [29]. In our case, medical treatment was partially effective. However, for fear of functional deterioration of the kidney because of the bilateral lesion, we could not increase the dosage of the calcium blocker, nor add angiotensin converting enzyme inhibitor. So, we chose to perform PTRA in our patient. Stent implantation was considered because stenotic lesion with pressure gradient remained after balloon angioplasty. Balloon expandable Palmaz® stents require additional dilatation in case of growth in the caliber of renal arteries, whereas oversized self-expanding LUMINEXX ® stents dilate in accordance to vessel growth. So, we chose LUMINEXX® stents, being advantageous in a growing young patient. PTRA with cutting balloon catheter might be an alternative modality, although its experience in pediatric patients is limited [35]. On the other hand, long term outcome might be dependent on the emergence of re-stenosis [25]. In our patient, PTRA with stenting was remarkably effective as shown by the decrease of blood pressure. However, the blood pressure became somewhat elevated 3 months after intervention, requiring increment of enalapril dosage. This might have resulted, in part, from intra-stent formation of neointima. So we should be carefully monitoring re-stenosis in our patient. This is also important because the etiology of arterial stenosis is still vague in our patient. Based on the arteriography findings of irregular wall of the stenotic lesion, fibromuscular dysplasia is the most probable etiology in our patient [34]. However, slight hypocomplementemia and elevation of anti-dsDNA antibody are potentially suggestive of future development of systemic lupus erythematosus. If so, the arterial stenosis might be progressive in nature unless the underlying disease is controlled by steroids or immunosuppressants. At present, because clinical and laboratory findings are devoid of active disease, we chose to wait and see without steroid administration, which could be the causative agent of thrombosis.

In summary, we experienced a case of RVH due to bilateral renal artery stenosis, and revascularization by PTRA with stent implantation was successfully performed. Although PTRA with stenting could be the choice of treatment modality even in pediatric patients with RVH, the efficacy and complication in the long term need to be carefully observed in the future.

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