Moyamoya disease with refractory hypertension associated with peripheral arterial stenosis in the renal parenchyma

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Abstract

Moyamoya disease (MMD) has long been known to be associated with hypertension. While renal artery stenosis (RAS) is considered one of the causes of hypertension with MMD, most hypertension causes remain unexplained. A boy with MMD was diagnosed with renovascular hypertension (RVH) due to left-sided RAS by angiography. Although nephrectomy on the affected side for unilateral RVH was performed, hypertension poorly improved. Histopathological examination of the resected specimens revealed that the vascular lumen not only of the renal artery but also of peripheral vessels in the renal parenchyma was narrowed. He developed end-stage renal disease caused by multiple wasp stings and received a kidney transplant from a living donor with his remaining right kidney resected. His hypertension improved dramatically just after the operation. In histopathological findings, the narrowed vascular lumen was also observed in the resected right renal parenchyma similar to that in the left kidney. In our case, these pathological findings were the same as those of major vessels previously reported in MMD patients. Immunohistochemical staining with anti-renin antibody on bilateral intrinsic kidneys was strongly revealed in the Juxtaglomerular apparatus. He has been normotensive with the minimum amount of amlodipine since transplantation and resection of his intrinsic right kidney. This is the first report to show the possibility that peripheral arterial stenosis in the renal parenchyma due to MMD would result in refractory hypertension. If MMD patients have hypertension of unknown origin without significant RAS, it should be considered that the etiology may be peripheral arterial stenosis in the renal parenchyma.

Keywords Histological finding · Hypertension · Moyamoya disease · Peripheral arterial stenosis · Renal parenchyma

Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive stenosis or occlusion at the terminal portions of the bilateral internal carotid arteries with a hazy vascular network at the base of the brain which is called moyamoya vessels [1]. The clinical presentations of

MMD include hemorrhagic stroke, ischemic stroke, transient ischemic attack, seizures, headaches, with varying frequency depending on age [2]. MMD can be complicated by renal artery stenosis (RAS), which can cause renal vascular hypertension (RVH) [3–7]. However, a recent study has found that in patients with MMD, hypertension not attributable to RAS is relatively common [8], and the cause of hypertension in MMD patients without RAS has not been identified.

We report the case of a patient with MMD who presented with systemic hypertension, which was thought to be caused by peripheral vascular stenosis in the renal parenchyma based on the clinical course and pathological findings.

Case report

A previously healthy 14-month-old boy whose mother had been diagnosed with MMD presented with suddenly decreased activity. At the emergency department, his vital

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sign revealed blood pressure (BP) 166/100 mmHg and he had right-sided hemiparesis with tendon hyperreflexia. A cranial computed tomography, magnetic resonance (MR) imaging, and MR angiography revealed hemorrhage in the posterior limb of the internal capsule and lateral ventricle, multiple infarctions, and disruption of blood flow at the terminal portions of the bilateral internal carotid arteries with moyamoya vessels, respectively (Fig. 1a). Cerebral angiography showed similar findings to MR angiography and he was diagnosed with MMD (Fig. 1b). Immediately after being diagnosed with MMD, indirect revascularization for stenosis of the bilateral internal carotid arteries was performed, but he was left with neurological sequelae such as hemiplegia and mental retardation. In addition, laboratory examination revealed marked hyperreninemia (plasma renin activity, 72 ng/mL/h) and hyperaldosteronemia (326 pg/mL) without electrolyte abnormalities, including hypokalemia, and urinary ones. Aortography revealed severe (> 75%) degree of stenosis at the proximal lesion of the left artery with the right intact one (Fig. 1c), which led to the diagnosis of RVH. Since antihypertensive medications, including nifedipine, amlodipine, lisinopril, and carvedilol, were not successful in improving RVH, percutaneous transluminal angioplasty (PTA) was performed. PTA relieved the degree

of stenosis and decreased BP by one step, but he could not discontinue his multidrug antihypertensive treatment. Subsequently, stenosis in the same area repeatedly worsened, and PTA was needed each time; however, it was difficult to control the BP. In the third episode, aortography revealed the complete disruption of blood flow in the left renal artery with a normal right artery (Fig. 1d), and captopril-loaded renal DTPA scintigraphy demonstrated the incompetence of the kidney ipsilateral to the obstructed renal artery. At the age of three, left nephrectomy was performed due to the difficulty in controlling RVH by medical treatment and the above findings. Histopathological examination of the resected renal artery revealed both eccentric intimal fibrous and muscular median thickening with irregular undulation of the internal elastic lamina. Similar findings were observed in smaller arteries of the renal parenchyma, such as the interlobar or interlobular arteries (Fig. 2a, b), which suggested that these changes could also be involved in his refractory hypertension. After nephrectomy, his BP was gradually suppressed, but hypertension, which required a high dose of 4 antihypertensive drugs, persisted.

At the age of 7 years, he developed end-stage renal disease (ESRD) requiring maintenance peritoneal dialysis after multiple wasp stings. Hypertension with multiple and high-dose antihypertensive medications persisted even with adequate dialysis. One year after the development of ESRD, he received a living kidney transplant from his father. Given the pathological findings in the left renal parenchyma and his clinical course of persistent hypertension, his remaining right kidney was simultaneously resected. As expected, his hypertension improved dramatically just after the kidney transplant and the resection of his intrinsic kidney even though every antihypertensive medication was discontinued. In histopathological findings of his intrinsic right kidney, a narrowed vascular lumen was observed from the interlobar to the interlobular arteries in the right renal parenchyma, which was similar to that in the left kidney, as we have surmised. The renal artery was pathologically intact (Fig. 2c, d). Immunohistochemical staining with anti-renin antibody on bilateral intrinsic kidneys revealed more strongly in the Juxtaglomerular apparatus than in the controls (Fig. 2e–h). His BP has been controlled well with minimum amount of amlodipine for 3 years since transplantation and resection of his intrinsic kidney.

Fig. 1 Imaging findings of intracranial blood vessels. MR angiography showed disruption of blood flow at the terminal portions of the bilateral internal carotid arteries (white arrows) (a) and cerebral angiography revealed stenosis at the terminal portion of the internal carotid artery (white arrowhead) with moyamoya vessels (b). Findings of aortography. The renal artery has severe stenosis (stenosis degree > 75%) at the proximal lesion (black arrow) without the right renal artery involvement at the onset of MMD (c). At the third restenosis, blood flow is disrupted from the proximal lesion of the left renal artery (black arrowhead) with a normal right artery (d)

Discussion

The mechanism of hypertension in MMD patients is unclear, but RAS has long been considered one of the major causes of hypertension. The stenosis or occlusion of the renal artery in MMD can occur bilaterally or unilaterally [4, 5] and is often located in the proximal lesion of the main branch,

Fig. 2 **a–d** Histological findings of the kidneys and the renal arteries. The interlobular artery (**a**) and the interlobular arteries (**b**) in the left kidney have intimal fibrous thickening, irregular undulation of internal elastic lamina without significant disruption and proliferation, and muscular median thickening, resulting in narrowing of those vascular lumen (**a, b**: Elastica Van Gieson staining, $\times 100$ and $\times 200$, respectively). The interlobular artery (**d**) in the right kidney had intimal fibrous thickening and irregular undulation of internal elastic lamina without significant findings in the right renal artery (**c**) (**c, d**: Hematoxylin Eosin staining and Elastica-Masson trichrome staining, $\times 40$ and $\times 400$, respectively). **e–h** Histological findings of renin staining in the kidneys in our case and controls. The bilateral kidneys in our case (**e, f**: left and right kidney, $\times 200$, respectively) have more strongly staining in the Juxtaglomerular apparatus compared to the kidneys of the controls who had been on ACE-I for a long time and who had been on hemodialysis for 4 years due to ESRD, respectively (**g, h** $\times 200$)

resulting in RVH [3, 9]. PTA is often considered one of the treatment options to control refractory hypertension due to RAS, but it is often challenging to manage BP [5]. Kuwayama et al. reported a case of MMD in which nephrectomy on the affected side was effective for refractory RVH [10]. On the other hand, in our case, even nephrectomy of the stenotic side was not sufficient to control hypertension, and resection of the remaining right kidney with the intact renal artery

might dramatically improve hypertension. It is noteworthy that peripheral arteries in the right renal parenchyma were histologically stenotic, despite the absence of pathological lesions in the right renal artery. These clinical and pathological facts suggest that peripheral vascular lesions in the right renal parenchyma may be involved in refractory hypertension. The positive findings of renin staining that our case has more enhanced renin activity than controls with angiotensin-converting enzyme inhibitor (ACE-I) or ESRD also support the above theory. Consequently, the mechanism of the refractory hypertension that persisted after left nephrectomy in our case is considered to be as follows: decreased renal perfusion due to peripheral vascular stenosis in the remaining right renal parenchyma, which was presumed to have existed before the left nephrectomy, would increase renin secretion from the Juxtaglomerular apparatus, resulting in the activation of the renin–angiotensin–aldosterone system.

MMD involves not only intracranial but also systemic vessels [9, 11], and some previous reports have shown the pathological findings of intracranial vessels and major extracranial vessels [12–14], except for the details about those of peripheral vascular lesions in the renal parenchyma. The main histological findings in stenotic lesions of intracranial vessels in MMD were fibrocellular thickening of the intima and irregular undulation of the internal elastic lamina, which were associated with stenosis or obstruction of the vessel lumen [13, 14]. Ikeda proved that, in MMD patients, the pathological findings of extracranial arteries, including renal, pulmonary, and pancreatic arteries were similar to those of the intracranial vessels [11]. In our case, the pathological findings of the peripheral vessels in the bilateral renal parenchyma were similar to those previously reported in patients with MMD, which indicated that these findings could be attributed to MMD. Further pathological analysis of the kidney tissue in MMD patients is essential to prove our suggestion.

In MMD patients, several mechanisms of hypertension other than RVH may be proposed. First, Cushing’s mechanism or the selfish brain hypothesis can be the pathophysiology of hypertension in MMD. Systemic hypertension develops to compensate for decreased cerebral blood flow and elevated cerebrovascular resistance drives hypertension [15]. The characteristic cerebral hemodynamics of MMD similar to these compensatory mechanisms may be involved in elevated BP. Second, the pathogenetic susceptibility or intrinsic component of MMD may be associated with hypertension. The p.R4810, which is a polymorphism of RNF213 and is often found in Japanese MMD, has been associated with systemic hypertension [16, 17] and may play a role in angiogenesis [18]. Patients with mutations in other genes such as GUCY1A and ACTA2, which are strongly associated with MMD, also showed systemic vasculopathy and associated with hypertension [19, 20]. In our case, indirect

revascularization for bilateral internal carotid artery terminal stenosis was immediately performed just after the diagnosis of MMD, and it should have improved cerebral blood flow and cerebral vascular resistance, which means that the Cushing's mechanism could not occur. On the other hand, the involvement of the pathogenetic susceptibility to systemic hypertension remains unknown in our case, as genetic analysis could not be performed because of his parents' disagreement. Lee et al. described that the prevalence of hypertension in pediatric MMD patients was 29.0%, of which less than 10% were attributed to RAS [8]. Our case suggests that peripheral vascular stenosis in the renal parenchyma, in addition to the above mechanism, could be involved in the pathogenesis of unexplained hypertension in patients with MMD.

In summary, this is the first report suggesting that peripheral vascular stenosis in the renal parenchyma may be involved in hypertension in pediatric patients with MMD based on clinical course and pathological findings. In patients with MMD, if there is concomitant hypertension of unknown origin, it should be considered that the etiology may be peripheral arterial stenosis in the renal parenchyma. Further pathological analysis of renal tissue in MMD patients is necessary to support our suggestion.

Declarations

Conflict of interest All the authors have declared that no conflict of interest exists.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (approval number at Hyogo Prefectural Kobe Children's Hospital, Rei 2-14) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents of the patient included in this study.

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