Ask-Upmark kidney in a girl with neurofibromatosis type 1

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Abstract

Ask-Upmark kidney (AUK) is a scarred segment of the kidney, characterized by formation of primitive tubular and glomerular structures, and sporadically diagnosed as a cause of hypertension (HTN). A 6-year-old girl with neurofibromatosis type 1 (NF1) and moyamoya syndrome had severe HTN. Based on past history, she had HTN at the age of 1.5 years. Laboratory examination revealed slightly elevated plasma and renal venous renin activity without lateralization. No evidence of pheochromocytoma, or coarctation of the aorta was found. Contrast-enhanced computed tomography (CT) showed an area of hypoperfusion in the upper and middle poles with reduced size of the right kidney. The results of dimercaptosuccinic acid scintigraphy were in accordance with those of contrast-enhanced CT. Selected renal arteriography revealed a paucity of peripheral vascularity in the same parts of the right kidney. In the absence of a history of urinary tract infection and vesicoureteral reflux by cystography, we presumed that the severe HTN may be due to segmental hypoplasia of the kidney, AUK, with a possible contribution from NF1. Although renal artery stenosis and pheochromocytoma are well-known causes of HTN in NF1, this case demonstrates that HTN can be caused by AUK in patients with NF1.

Keywords Hypertension · Renal scarring · Neurofibromatosis type 1 · Ask-Upmark kidney

Introduction

Hypertension (HTN) was reported to be present in 16–20% of pediatric patients with neurofibromatosis type 1 (NF1) [1, 2]. Renal artery stenosis (RAS) and pheochromocytoma are important for the differential diagnosis of HTN in NF1. NF1 vasculopathy is related to HTN, by inducing RAS, coarctation of the aorta, and other vascular lesions [3]. NF1 vasculopathy was also suggested to be related to HTN without structural lesions via altered arterial distensibility [1, 4].

Renal scarring (RS), occasionally identified on abdominal computed tomography (CT) scans incidentally, might be associated with HTN [5]. RS can be acquired or congenital. Acquired RS is related to urinary tract infection (UTI) commonly associated with vesicoureteral reflex (VUR), trauma, or infarction, while congenital RS includes hypoplasia and

dysplasia. One form of RS called segmental renal hypoplasia is also known as Ask-Upmark kidney (AUK) [6], which is sporadically diagnosed as a cause of severe HTN, especially in pediatric and adolescent populations [7–10].

Here, we report a case of a 6-year-old girl with NF1 and moyamoya syndrome who presented with HTN and RS compatible with AUK. We presumed that severe HTN was caused by AUK with a possible contribution from NF1 vasculopathy.

Case report

A 6-year-old girl was referred to our hospital with HTN. She consulted a local pediatrician due to proteinuria detected by a school urine screening program. At presentation, she was hypertensive (160/110 mm Hg). The interview disclosed that the patient had intermittent left frontal headache for 3 days before admission without nausea, vomiting or visual changes. At the age of 1.5 years, she was seen by a local physician due to 2+ proteinuria and 1+ hematuria detected by her nursery school urine screening program. She had slightly elevated blood pressure (96/74 mmHg), along with a urinary protein to creatinine ratio of 0.56 (g/g creatinine,

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g/g Cr). However, she had not been followed-up thereafter. She had no history of UTI. She was the only child of non-consanguineous parents. Her father had café-au-lait spots.

On physical examination, her height was 108.5 cm (− 1.2 SD), body weight was 18.0 kg (− 0.5 SD), pulse was 104 beats per minute, and respiration rate was 18 breaths per minute. Her blood pressure was 167/111 mm Hg in the right arm, 168/125 mmHg in the left arm, 168 mm Hg in the right leg, and 162 mmHg in the left leg. She had more than six café-au-lait spots larger than 5 mm in diameter and freckling in the groin and axilla area. Ophthalmologic examination revealed no Lisch nodules of the iris or hypertensive changes. The remainder of the physical examination was normal including neurological examination.

Urinalysis showed 2+ proteinuria with a urinary protein to creatinine ratio of 1.40 g/g Cr. Urinary blood, glucose, cells, and casts were not detected. Serum total protein was 7.5 g/dL, albumin was 4.8 g/dL, and creatinine was 0.33 mg/dL, with all other blood parameters in the normal range. The plasma renin activity (PRA) and serum aldosterone levels were 9.7 ng/mL/h and 248.0 pg/mL, respectively, in a recumbent position after rest (normal values 0.2–2.3 ng/mL/h and 20–130 pg/mL, respectively). The serum levels of thyrotropin, thyroxine, free thyroxine, adrenocorticotrophic hormone, and cortisol, as well as urinary catecholamines were normal.

On echocardiography, her left ventricular function was normal and left ventricular wall thickening was not detected. Cerebral magnetic resonance (MR) imaging and angiography to screen cerebral lesions of NF1 showed an unidentified bright object and moyamoya syndrome (Fig. 1a). There was no radiological evidence of a tumor. A renal ultrasonography (US) showed that the diameters of the right and left kidneys were 6.6 cm and 7.2 cm. Both renal parenchyma appeared normal. However, contrast-enhanced CT showed RS in the upper pole and hypo-density in the middle of the right kidney (Fig. 1b, c). A dimercaptosuccinic acid (DMSA) scintigraphy revealed decreased uptake in the same regions (Fig. 1d), and the ratio of the right-left kidney function was 40%. An angiography showed two left renal arteries and one right renal artery without evidence of stenosis. Selected renal arteriography revealed a paucity of peripheral vascularity in the upper pole and medial portion of the right kidney (Fig. 1e). Renal vein sampling showed a PRA of 6.6 ng/mL/hr in the right renal vein, 6.8 ng/mL/hr in the left renal vein, and 7.1 ng/mL/hr in the inferior vena cava.

To rule out postpyelonephritic RS, we performed a voiding cystourethrogram, which revealed no VUR. On the basis of her clinical history and radiological findings, we diagnosed her RS as segmental renal hypoplasia, i.e. AUK. Her blood pressure was controlled at approximately 110/70 mmHg with amlodipine and enalapril, without any surgical procedures.

Discussion

Renal segmental hypoplasia or AUK, first described in 1929 by Erik Ask-Upmark [7], is infrequently diagnosed as a cause of HTN [7–9]. It is a localized area of arrested nephrogenesis, which creates a deep transverse groove (scar) on the cortical surface and dilatation of the corresponding calyces [9]. Histological studies revealed a sharp demarcation between the grooves and the adjacent grossly normal cortex. Atrophic foci contained colloid cast containing tubules, numerous vessels with thickened walls, and rare or no glomeruli [7–9]. Previously, a definitive diagnosis of AUK was based on pathological findings at nephrectomy or autopsy. The improved medical management of HTN, however, has made the surgical procedure unnecessary and allowed the diagnosis of AUK to be based on radiological and clinical findings [9–11].

Our patient, a 6-year-old girl with NF1, had severe HTN during the investigation of chance proteinuria. Given that she had a history of proteinuria and elevated blood pressure at the age of 1.5 years, it is possible that she had been hypertensive since then, although there was no evidence suggesting chronic hypertension such as cardiac or ophthalmological findings. A contrast-enhanced CT revealed RS lesions containing a thin cortex overlying the dilated calyx in the upper pole of the right kidney, and a DMSA scan revealed decreased uptake. These findings are compatible with AUK. Elevation of peripheral PRA suggested a renal etiology, although there was no lateralization of renal vein renin values. Increased renin levels have been reported to be the mechanism of HTN in AUK, partly based on the normalization of blood pressure following nephrectomy. The lateralization of renal vein renin levels, however, was not universally observed as in our case [9, 10].

Although AUK was originally described as a congenital defect in the development of the renal vasculature, it has a high association with VUR and pyelonephritis [9, 12]. We assumed that in our patient, RS had existed at 1.5 years of age. While the young age may suggest a congenital etiology, acquired etiologies for RS including VUR and pyelonephritis were not completely excluded, even in the absence of a history of UTI and VUR at the current age of 6 years.

Royer et al. in 1971 [11] described that 14 of 36 cases of AUK had renal artery lesions, of which six were simple anomaly, such as arteriovenous fistula, arterial aneurysms, and fibromuscular dysplasia of renal artery. Multiple abnormalities were observed in eight other patients, in which lesions of renal arteries were associated with multiple stenosis (coarctation of the abdominal aorta, subclavian artery), aneurysms, or thrombosis in various

Fig. 1 Kidney imaging. **a** Cerebral MR angiography. The arrow shows an occlusion of the right medial cerebral artery. **b** Abdominal contrast-enhanced CT image during the excretory phase. An area of hypoperfusion is shown containing a thin cortex overlying the dilated calyx in the upper pole of the right kidney. The arrow indicates the groove separating the lesion. There is also a perfusion defect in the middle of the right kidney (arrowhead). **c** Anterior view of a 3-dimensional image reconstructed from spiral computed axial

tomography. A segmental area of hypo-density in the upper pole of the right kidney is shown (arrow), along with a wedged shaped hypo-density area in the middle of the right kidney (arrowhead). **d** DMSA scintigraphy. The image shows decreased uptake (arrow) at the upper pole of the right kidney by anterior view. **e** Renal arteriography. Selected renal arteriography shows a paucity of peripheral vasculature in the upper pole (arrow) and the middle (arrowhead) of the right kidney without stenosis in the main right renal artery.

sites. Three were associated with NF1. Subsequently, case reports accumulated describing the coexistence of AUK and vascular lesions, such as renal and extrarenal arterial aneurysms [10], fibromuscular dysplasia [14], or congenital abnormalities [15]. These previous reports suggested a primary vasculopathy is the cause of the renal hypoplastic

renal arteries of AUK. Therefore, we think that NF1 vasculopathy have significantly contributed to the development of AUK in our patient.

NF1 vasculopathy is well known and affects blood vessels of various sizes ranging from the aorta to small arterioles [3]. The lesions are patchy in distribution, but multiple

vessels are frequently involved, characterized by vascular smooth muscle cell (VSMC) accumulation in the intima area of vessels resulting in vascular stenosis and occlusion [3]. Neurofibromin, the protein product of NF1 normally expressed in vascular epithelial cells and VSMC, regulates cell growth through Ras regulation, and therefore, is likely to be involved in the pathogenesis of NF1 vasculopathy [3]. An in vivo study reported that *Nf1* heterozygous (*Nf1*^{+/-}) mice had increased neointima formation, excessive vessel wall cell proliferation and extracellular signal-regulated kinase activation after vascular injury [3]. *Nf1*^{+/-} macrophages produced excessive reactive oxygen species, which enhanced *Nf1*^{+/-} smooth muscle cell proliferation in vitro and in vivo [16]. In our case, the presence of moyamoya syndrome suggested the presence of NF1 vasculopathy. In addition to RS in the right kidney, another defect in the middle of the right kidney was revealed by 3D reconstructed CT images, which may be ascribed to vascular occlusion rather than infection. Moreover, selected renal arteriography showing a paucity of peripheral vascular in lesions of the right kidney might also represent vascular occlusion in which the ostium of the vessel is of normal size and the distal vessel tapers in caliber [10]. Overall, we speculate that AUK in our case was secondary to NF1 vasculopathy.

In conclusion, we experienced a case of NF1 with AUK. This report suggests a potential role of NF1 vasculopathy in the etiology of AUK.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As per Seirei-Mikatahara General Hospital research ethics board recommendation, written “consent to be included in a report” was obtained from the parent of the infant in this report. The consent form states that information about the child’s illness will be published.

References

1. Tedesco MA, Di Salvo G, Ratti G, Natale F, Calabrese E, Grassia C, Iacono A, Lama G. Arterial distensibility and ambulatory blood pressure monitoring in young patients with neurofibromatosis type 1. *Am J Hypertens*. 2001;14:559–66.
2. Dubov T, Toledano-Alhadeff H, Chernin G, Constantini S, Ben-Shachar S, Cleper R. High prevalence of elevated blood pressure among children with neurofibromatosis type 1. *Pediatr Nephrol*. 2016;31:131–6.
3. Kaas B, Huisman TAGM, Takes A, Bergner A, Blakeley JO, Jordan LC. Spectrum and prevalence of vasculopathy in pediatric neurofibromatosis type 1. *J Child Neurol*. 2013;28:561–9.
4. Ueda K, Awazu M, Konishi Y, Takenouchi T, Shimoizato S, Kosaki K, Takahashi T. Persistent hypertension despite successful dilation of a stenotic renal artery in a boy with neurofibromatosis type 1. *Am J Med Genet*. 2013;161A:1154–7.
5. Fidan K, Kandur Y, Buyukkaragoz B, Akdemir UO, Soylemezoğlu O. Hypertension in pediatric patients with renal scarring in association with vesicoureteral reflux. *Urology*. 2013;81:173–7.
6. Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. *J Urol*. 2010;184:265–73.
7. Ask-upmark E. About juvenile malignant nephrosclerosis and their relationship to disturbances in renal development. *Acta Path Microbiol Scand*. 1929;6:383–442.
8. Babin J, Sackett M, Delage C, Lebel M. The Ask-Upmark kidney: a curable cause of hypertension in young patients. *J Hum Hypertens*. 2005;19:315–6.
9. Arant BS Jr, Sotelo-Avila C, Bernstein J. Segmental, “hypoplasia” of the kidney (Ask-Upmark). *J Pediatr*. 1979;95:931–9.
10. Marwali MR, Rossi NF. Ask-Upmark kidney associated with renal and extrarenal arterial aneurysms. *Am J Kidney Dis*. 1999;33(4):E4.
11. Royer P, Habib R, Broyer M, Nouaille Y. Segmental hypoplasia of the kidney in children. *Adv Nephrol*. 1971;1:145–59.
12. Sheinman JJ, Crevi DL, Narla LD, Chan JC. Asymptomatic childhood hypertension. *Nephron*. 1998;79:131–6.
13. Shindo S, Bernstein J, Arant BS Jr. Evolution of renal segmental atrophy (Ask-Upmark kidney) in children with vesicoureteric reflux: radiographic and morphologic studies. *J Pediatr*. 1983;102:847–54.
14. Bonsib SM, Meng RL, Johnson MF Jr. Ask-Upmark kidney with contralateral renal artery fibromuscular dysplasia. *Am J Nephrol*. 1985;5:450–6.
15. Zenzulka AV, Arkell DG, Beevers DG. The association of hypertension, the Ask-Upmark kidney and other congenital abnormalities. *J Urol*. 1985;12:1000–1.
16. Bessler WK, Hudson FZ, Zhang H, Harris V, Wang Y, Mund JA, Downing B, Ingram DA Jr, Case J, Fulton DJ, Stansfield BK. Neurofibromin is a novel regulator of Ras-induced reactive oxygen species production in mice and humans. *Free Radic Biol Med*. 2016;97:212–22.

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