An unusual cause of renovascular hypertension in a pediatric patient with chronic kidney disease

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Abstract

Background: Renovascular hypertension (RVH) accounts for 5–10% of arterial hypertension in children and is most commonly caused by fibromuscular dysplasia. Sporadically, renal artery stenosis in pediatric patients is caused by extrinsic compressive masses.

Case report: A 12-year-old patient with complex urinary tract defect (dysplastic left kidney — nephrectomy at 11 months, right ectopic kidney in the midline, behind the urinary bladder), chronic kidney disease (CKD) stage 2, and arterial hypertension was admitted to the hospital due to worsening of kidney function during angiotensin-converting enzyme inhibitor (ACE-I) therapy. CT angiography revealed a right ectopic kidney located above the bladder, supplied by a single renal artery originating from the right common iliac artery. The renal artery had a tortuous shape with width in the ostium approx. 4.5 mm; then, the artery was bent and ran between the common iliac artery and the kidney. Ultrasound performed with a filled bladder showed bending and stenosis of the renal artery at the origin from the right common iliac — peak systolic velocity (PSV) 4.5–5.5 m/s and renal-aortic ratio (RAR) 3.1. With an empty bladder, no bending or stenosis was visible (PSV 1.7–1.9 m/s and RAR 1.0). Uroflowmetry revealed a dysfunctional micturition curve, large bladder capacity, and post-void urine retention. ACE-I was changed to beta-blocker and doxazosin, which led to blood pressure and kidney function normalization.

Conclusions: Renal ectopia associated with bladder dysfunction may result in renal artery stenosis causing renovascular hypertension.

Key words: renovascular hypertension; renal ectopia; chronic kidney disease; bladder dysfunction; adolescent

Arterial Hypertens. 2022, vol. 26, no. 2, pages: 92–97
DOI: 10.5603/AH.a2022.0009

Introduction

Arterial hypertension (AH) is a serious public health problem, as it is the most important risk factor of cardiovascular morbidity and mortality [1]. It affects about 3–5% of children and adolescents, and from puberty, its prevalence increases and occurs 3–4 times more often in boys than in girls [2]. Nowadays, due to the epidemy of obesity, sedentary lifestyle, and excessive dietary sodium intake, a significant increase in primary hypertension is observed [3]. However, in the pediatric population, second-

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ary hypertension is still the leading cause, most often in the course of renal parenchymal diseases and renal artery stenosis [2–4].

Renovascular hypertension (RVH) comprises 5–10% of cases of pediatric hypertension [5]. The most common cause of RVH in pediatric patients is fibromuscular dysplasia in Europe and North America and Takayasu arteritis in Asia and Africa [6–8]. Other causes of RVH include renal artery thrombosis (e.g., as a consequence of renal artery catheterization), congenital stenosis/hypoplasia of the renal artery, neurofibromatosis type 1, tuberous sclerosis complex, Williams-Beuren, Alagille, and Grange syndromes, other forms of arteritis (e.g., polyarteritis nodosa), and extrinsic compressive masses [2, 5, 7–9]. Renal artery stenosis rarely accompanies urinary tract malformations, with only single cases reported [10]. We present a case of a teenage boy with stenosis of a renal artery supplying solitary ectopic kidney caused by urinary bladder dysfunction.

Case report

A 12-year-old boy with a complex urinary tract malformation, chronic kidney disease (CKD) stage 2, and AH was admitted to the hospital due to deterioration of kidney function. The prenatal examination revealed an absence of the right kidney in the typical position and abnormalities in the left urinary tract and kidney for further differentiation (polycystic kidney or hydronephrosis). Shortly after he was born, the left kidney was found to be typically positioned, enlarged (75 mm), and dysplastic with multiple cysts. The right ectopic kidney was located at the level of L4-L5 (lumbar vertebrae) in the body's midline, behind the bladder, with incomplete rotation and persistent fetal lobulation. In urography, the contrast agent secretion of the right kidney was normal, and the secretory function of the left kidney was absent. Voiding cystourethrography (first week of life) revealed passive and active vesicoureteric reflux (grade 2–3) to the right kidney. Dynamic scintigraphy revealed diminished uptake and slow contrast release from the left kidney (left kidney — 23%, right kidney — 77%). At the age of 11 months, a left-sided nephrectomy was performed.

At the age of eight, the patient's creatinine was 0.9 mg/dL (GFR according to Schwartz formula [11] – 62 mL/min/1.73m^2), the patient was diagnosed with CKD stage 2. At that point, 24-hour ambulatory blood pressure monitoring was performed — 24 h mean arterial pressure was between 95–99th percentile during the day and above 99th percentile at night — enalapril 2 × 2.5 mg was implemented.

In the outpatient clinic, due to poor control of AH (blood pressure up to 150/70 mm Hg), enalapril was changed to ramipril and then to lisinopril (initially 5 mg, then 10 mg once daily). Because of the increase in creatinine concentration during treatment with angiotensin-converting enzyme inhibitor (ACE-I) to 1.1 mg/dL [glomerular filtration rate (GFR) 61.5 mL/min/1.73 m^2], the boy was referred to our tertiary center of pediatric nephrology with suspicion of RVH.

The boy was hospitalized in our Department at the age of 12.5 years. His physical examination was unremarkable, his height (164 cm — 75–90 percentile according to [12]) and weight (62 cm — 90 percentile acc. to [12]) were within normal limits, his office blood pressure was 139/75 – 142/84 mm Hg (above 95 percentile [13]), his creatinine was 1.1 mg/dL (GFR — 61.6 mL/min/1.73 m^2), urea — 53 mg/dL; urinalysis was normal except for low specific gravity, and urinary albumin loss was 80 mg/24 h.

In CT angiography (Fig. 1), the right ectopic kidney was located above the bladder, with incomplete rotation, supplied by a single renal artery that originated anteriorly from the right common iliac artery, below the bifurcation. The artery had an irregular, tortuous shape. The width of the artery in the ostium was about 4.5 mm; then, the artery was bent and ran between the common iliac artery and the kidney (the kidney was modeled at this level).

The ultrasound performed with a filled bladder showed the bending and stenosis of the renal artery at the origin of the right common iliac artery. In the Doppler ultrasonography (Fig. 2), peak systolic velocity (PSV) was 4.5–5.5 m/s, and renal-aortic ratio (RAR) was 3.1. With an empty bladder (Fig. 3), no bending or stenosis was visible, and in the Doppler ultrasonography, there were no features of stenosis: PSV was 1.7–1.9 m/s and RAR — 1.0.

The boy was complaining about rare urination. A uroflowmetry revealed the dysfunctional micturition curve, large bladder capacity (470 mL), and post-void residual urine retention (40 mL). As the kidney function was deteriorating, ACEi was stopped. The treatment was changed for extended-release metoprolol (50 mg, once daily) with doxazosin (2 × 1.0 mg) — the latter was chosen due to bladder dysfunction. Due to hyperuricemia (9.4 mg/dL), allopurinol (100 mg, once daily) was started. After administering the beta-blocker and doxazosin, blood pressure normalized and creatinine concentration decreased to 0.9 mg/dL (GFR 75.3 mL/min/1.73 m^2), the voiding frequency improved.

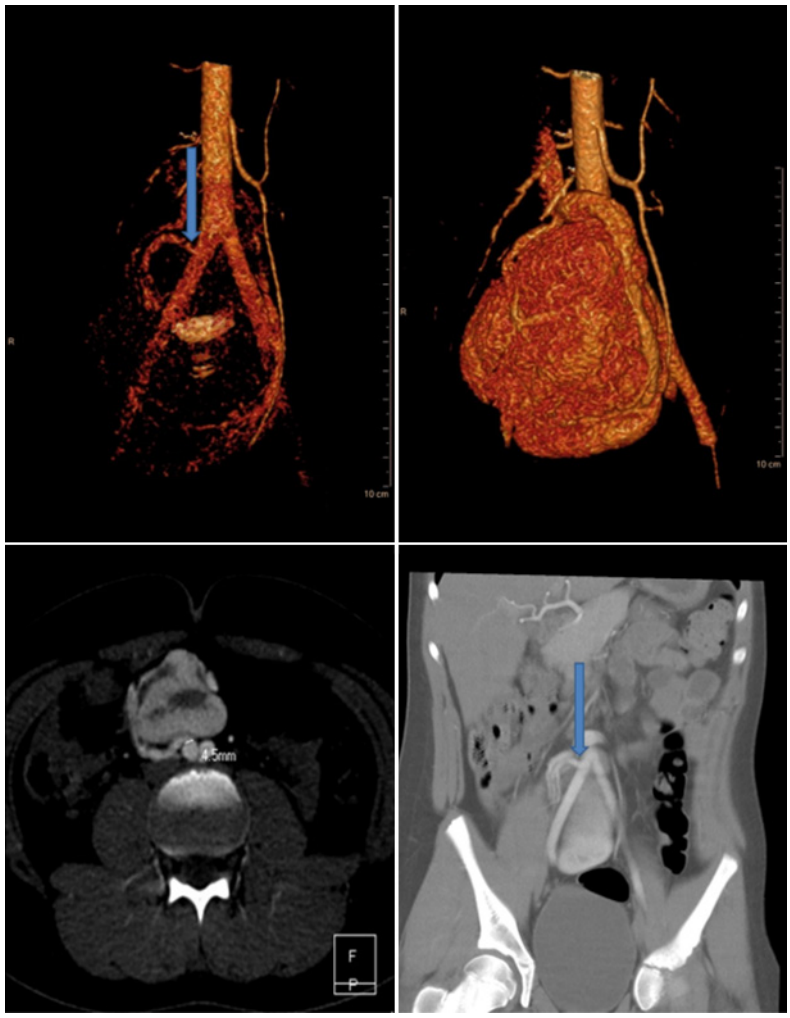

Figure 1. A computed tomography (CT) angiography: right renal artery arising from the right common iliac artery with the bending and compression between the urinary bladder, right kidney, and right common iliac artery (blue arrow — bending of the right renal artery)

Due to concurrent urinary tract malformation, hyperuricemia, and periodical hypomagnesemia (1.5 mg/dL), *HNF1B* (hepatocyte nuclear factor-1-beta) mutation was suspected, but the genetic test (next-generation sequencing, NGS) was negative.

At present, the boy is 15 years old, his creatinine is 1.1 mg/dL (GFR — 65.3 mL/min/1.73 m^2), blood pressure is well controlled (114/70 mm Hg) on doxazosin 2 × 1 mg.

Discussion

We present a case of renovascular hypertension, in whom the stenosis of the renal artery supplying ectopic kidney was caused by bladder dysfunction. Interestingly, the filling of the bladder with urine had a significant effect on anatomical relations and stenosis — Doppler ultrasound examination revealed abnormal blood flow to the kidney only with the urinary bladder filled. As in every case of renal artery stenosis of a solitary kidney, treatment with ACEi impaired renal function. Of note, the blood pressure and kidney function stabilized once the patient was started on alpha-adrenolytic, which also acted on bladder function.

The patient has been diagnosed with a lumbar kidney located at the level of L4–L5, which reported incidence is 12% in all ectopic kidneys. In contrast, the most common pelvic ectopia constitutes 55% of all ectopic kidneys [14]. Most renal ectopia is asymptomatic, but it can present as urinary tract infections, abdominal pain, hematuria, urinary incontinence, and hypertension [15]. The symptoms can be helpful in diagnosis, but most often, the final diagnosis is made postnatally by abdominal ultrasonography and confirmed by a static 99m technetium dimercaptosuccinic acid (DMSA) scan [15]. Our patient had prenatal suspicion of a complex urinary tract defect. Postnatally, the final diagnosis was made with a com-

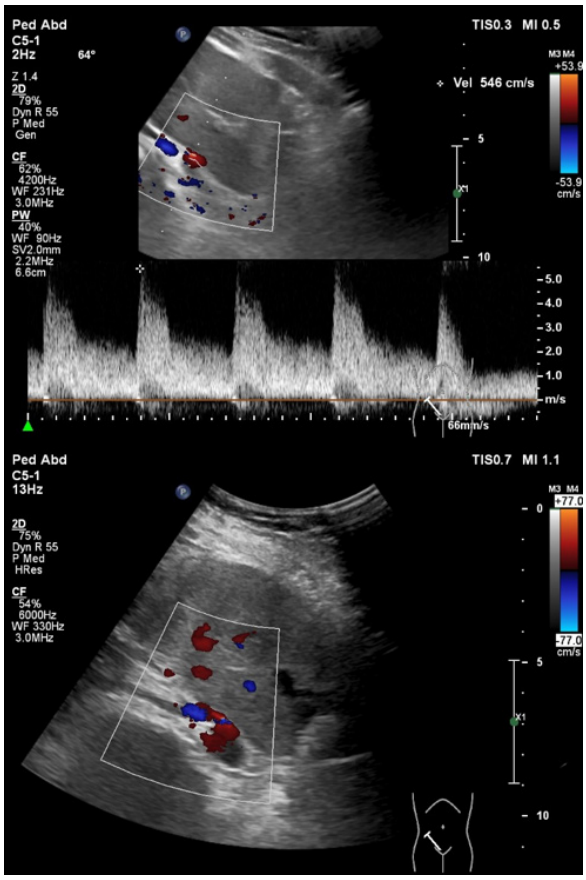

Figure 2. Doppler ultrasonography of renal artery with a filled bladder: right renal artery arising from the right common iliac artery with the bending and peak systolic velocity (PSV) 5.5 m/s.

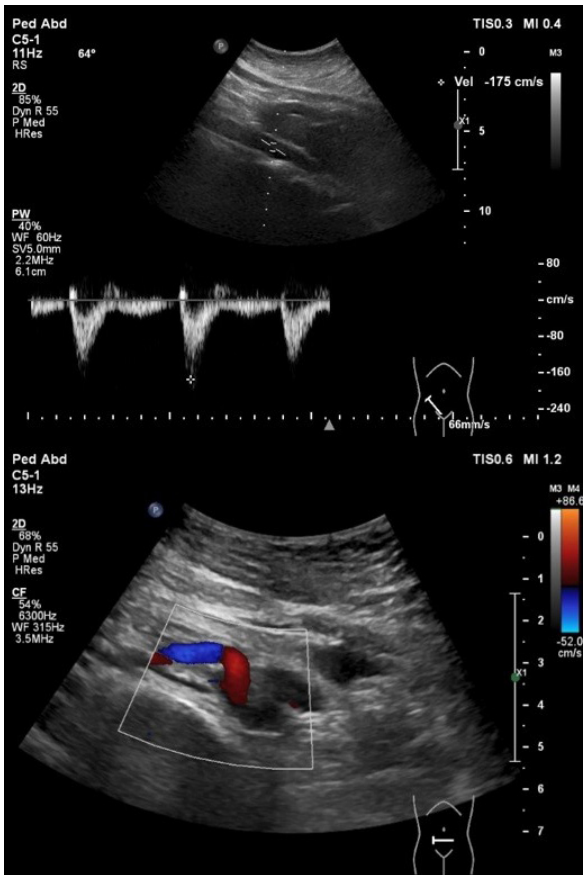

Figure 3. Doppler ultrasonography of renal artery with an empty bladder: no bending or stenosis visible

bination of imaging modalities (i.e., ultrasonography, voiding cystourethrography, urography, and renal scintigraphy). Renal ectopia can coexist with other congenital urinary anomalies, of which vesicoureteral reflux is the most common one [15–17]. Its frequency ranges from 2 to 70 % in various studies; in most, it is reported at approx. 20% [15, 17]. Apart from VUR, renal ectopia can coexist with hydronephrosis, contralateral renal dysplasia, multicystic dysplastic kidney, and renal agenesis [15, 18]. The blood supply of the ectopic kidneys varies, and the renal artery usually originates from the nearest large vessels such as the common iliac artery or aorta [19]. In our patient the single renal artery arose from the right common iliac artery, just below the bifurcation.

Our patient developed AH, similar to 3.5% of patients with renal ectopia, as Mininberg et al. [18] reported. In turn, other studies didn't show increased blood pressure in the course of renal ectopia [16, 17]. The treatment of AH in our patient was initiated by implementing angiotensin-converting enzyme inhibitors. According to the American Academy of Pediatrics 2017 and European Society of Hypertension guidelines, ACE inhibitors or angiotensin II receptor blockers (ARB) are medications of choice in patients with CKD and AH [2, 4]. In line with the ESCAPE study, present guidelines recommend lowering blood pressure in CKD patients much below the 90th percentile. In recent KDIGO guidelines, target BP is as low as below the 50th percentile [20].

Urinary tract defects, hyperuricemia, and hypomagnesemia suggest the presence of *HNF1B* mutation. The result of the genetic test was negative. Of note, NGS cannot categorically exclude *HNF1B* gene defect, and further patient follow-up is mandatory. Mutation of the *HNF1B* gene is typically responsible for bilateral renal cystic hypodysplasia, hyperuricemia, elevated liver enzymes, and diabetes mellitus [21]. Moreover, in some patients, it manifests with hypomagnesemia due to impaired reabsorption of magnesium in the distal tubule (Gittelman-like phenotype) [21, 22].

Fibromuscular dysplasia is a leading cause of RVH in young people, including pediatric patients. FMD can be found even in infants. In children, FMD is characterized by a high prevalence of extrarenal artery involvement [23]. However, the clinician should not

forget the rare forms of RVH. Etiologic and differential diagnosis matters both for prognosis and management, as illustrated in a recent review by Persu et al. [9].

The unique feature of our patient was the origin of the renal artery stenosis. Doppler ultrasonography revealed that the filled bladder contributed substantially or even caused renal artery stenosis. Noteworthy, the patient was found to have urinary bladder dysfunction with rare micturition, increased bladder capacity, post-void urine retention, and dysfunctional micturition curve. Alpha-adrenergic receptor antagonist (doxazosin) therapy was started, and urotherapy was implemented, which resulted in increased voiding frequency and stabilization of blood pressure and renal function. Alpha-adrenergic receptor antagonists relax the smooth muscle at the bladder neck and proximal urethra. They are widely used in neurogenic and non-neurogenic bladder dysfunction in both adults and children [24, 25]. Doxazosin with non-specific action also on vascular smooth muscle cells was chosen to lower systemic bladder. Noteworthy, both adult and pediatric guidelines do not recommend alpha-adrenolytics as first-line medications without other comorbidities [1, 2].

RVH can be caused by renal artery compression by extrinsic masses, e.g., Wilms' tumor, neuroblastoma, renal cysts, or diaphragmatic crura [8, 26]. To the best of our knowledge, this is the first reported case of RVH caused by renal artery displacement and compression by dysfunctive urinary bladder. Conversely, bladder dysfunction was revealed in an experimental model of renovascular hypertension with tissue remodeling and enhanced muscarinic M(3)-mediated contractions associated with reduced beta-adrenoceptor-mediated signal transduction [27]. The same authors showed bladder function improvement with losartan and captopril [28]. Jeronimo et al. reported a case of a 13-month-old baby with severe RVH (bilateral renal artery stenosis) that manifested with failure to thrive, recent muscular weakness of the lower extremities, and irritability. In the authors' opinion, the patient was diagnosed with a neurogenic bladder that was most probably caused by medullary infarction caused by severe hypertension [29]. In the presented case, due to renal function, blood pressure stabilization, and extremely difficult surgical conditions and access, the patient was treated conservatively.

Conclusions

Renal ectopia associated with bladder dysfunction may result in renal artery stenosis causing renovascular hypertension.

Institutional Review Board Statement

The Local Bioethics Committee approved the study (Approval Code: AKBE/200/2021). Informed consent was obtained from the patient's representatives for publishing the study.

Funding

This research was funded from the statutory funds of the Department of Pediatrics and Nephrology, Medical University of Warsaw.

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