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## Case Report

# Multimodal imaging approach in hyponatremic hypertensive syndrome. A rare case of pediatric unilateral hypoplasia of the main renal artery combined itself with stenosis and review of literature <sup>☆</sup>

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## ABSTRACT

Renal artery stenosis (RAS) accounts for approximately 5%-10% of secondary renovascular hypertension in the pediatric population. It can occur as an isolated entity, or as a hypoplasia combined itself with stenosis. Hypoplasia, or long-segment developmental narrowing, is a rare cause of renovascular hypertension. Hyponatremic hypertensive syndrome (HHS) is a malignant complication of unilateral RAS and/or renal artery hypoplasia. Hyponatremia, hypokalemic hypochloremic metabolic alkalosis, nephrotic range proteinuria, polyuria, polydipsia, and weight loss are the most common findings. In particular, hypertension remains refractory despite aggressive antihypertensive therapy. Laboratory findings of elevated plasma levels of renin in most case suggest that the stimulation of renin release from the ischemic kidney plays an important pathophysiologic role. HHS is a diagnostic and therapeutic challenge in children. We report a case of a unilateral right renal artery hypoplasia, complicated by a segmental narrowing, in a 17-month-old male, clinically symptomatic for hypertension. We emphasize the role of ultrasound, computed tomography, and digital

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subtraction angiography that should be planned as reliable and non-invasive multimodal imaging approach.

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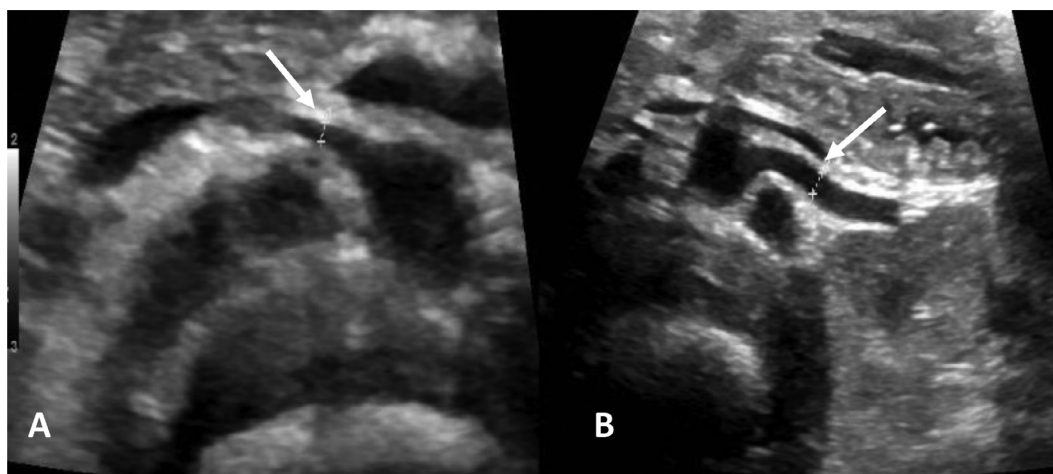
## Introduction

Pediatric renovascular hypertension is a complex disorder that can be caused by various conditions [1–6]. Renal artery stenosis (RAS) accounts for approximately 5%–10% [7] of secondary renovascular hypertension (RVH) in the pediatric population. It is often asymptomatic but severe yet asymptomatic. RAS can occur as an isolated entity, or as a hypoplasia combined itself with stenosis. Hypoplasia, or long-segment developmental narrowing, is a rare cause of RVH [8,9]. Hyponatremic hypertensive syndrome (HHS) is a malignant complication of unilateral RAS and/or renal artery hypoplasia. Nicholls [10] sustained that it is underdiagnosed and probably more common than previously thought. It can be clinically suspected when plasmatic levels of renin and aldosterone are high in values, in association with hyponatremia, hypokalemic hypochloremic metabolic alkalosis, nephrotic range proteinuria, polyuria, polydipsia, dehydration and weight loss. In particular, hypertension remains refractory despite aggressive antihypertensive therapy. The underlying pathophysiological mechanism consists in activation of the renin-angiotensin system caused by a reduced blood flow to—a part or all—one or both kidneys: it results in vasoconstriction and sodium/fluid retention induced by aldosterone leading to increased blood pressure, eventually. HHS is a diagnostic and therapeutic challenge in children. Imaging is crucial in confirming the early diagnosis [5,6,11–14] since interventional treatment may improve or cure hypertension and preserve renal function [15]. In all instances, a multi-disciplinary team approach should be used to provide optimal care and life expectancy in children. The present study reported a rare case of a unilateral right renal artery hypoplasia, complicated by a segmental narrowing, in a 17-month-old male clinically symptomatic for HHS. US first and, CT/DSA then, were practiced in order to compare and integrate different imaging modalities.

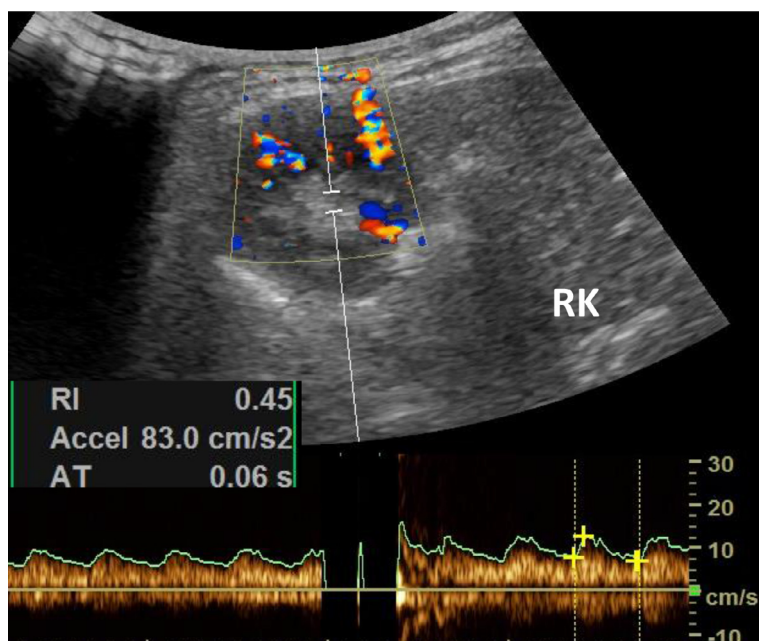
## Case report

A 17-month-old male was admitted to our Pediatric Emergency Room for persistent vomiting and diarrhea. During hospitalization, the little patient showed increased plasmatic levels of renina (29.7 ng/mL/h) and aldosterone (>100 ng/dL) in association with severe hyponatremia, hypokalemic hypochloremic metabolic alkalosis, nephrotic range proteinuria, polyuria, polydipsia, dehydration, and weight loss. In particular, hypertension remained refractory despite aggressive antihypertensive therapy. Familiar history was unremarkable for renal or vascular diseases. As first ap-

proach, we performed a targeted urinary tract ultrasound examination. Both kidneys resulted in their anatomical site, but the left was predominant. The gray scale already revealed a caliber asymmetry in renal arteries (Fig. 1): the right renal artery had a reduced diameter (0.9 mm) if compared to the opposite one (1.9 mm). A further pulsed Doppler evaluation demonstrated the right interlobar artery resistive index significantly lower than the norm (RI 0.45) with an increased acceleration time, so a “parvus et tardus” waveform was detected (Fig. 2). The left interlobar artery resistive index, instead, was within normal limits (RI 0.69) in absence of pulsus alterations (Fig. 3). These specific US features were consistent with a unilateral main renal artery “hypoplasia” that could be the trigger event for renal volume change and hemodynamic chain-reaction sequelae, a very probably cause and/or contributing cause in turn for RVH. In view of likely interventional recovery procedures to correct a suspected stenosis, a computed tomography (CT) was just planned. The right kidney was significantly decreased in size - right long axis R: 48 mm versus left long axis L: 72 mm (Fig. 4) and a low enhancement was appreciated. The right renal artery caliber confirmed itself half than the contralateral (1 mm vs 2.1 mm). Additionally, a segmental narrowing, placed about 6 mm from abdominal aorta diramation for a maximum extension of approximately 4 mm. A right filiform accessory renal artery, originating just above the main vessel, was also founded (Figs. 5A, 6A, 6B). Left kidney was regular in morphology and size with a preserved excretory function and an omolateral homogeneous renal artery. Nothing to report, except for the presence of a left accessory renal artery: it had a smaller caliber and a caudal emergence in relation to the main artery (Figs. 5B, 6A, 6B). Bilaterally, no evidence of dilation in ureters, bladder, and urethra. The day after, our child underwent a puncture of the right common femoral artery and aortic catheterization. The digital subtraction angiography (DSA) showed a preocclusive stenosis at the third medium of the pathological vessel. The obstacle was overcome and the percutaneous transluminal angioplasty (PTA) reached the correct final dilation, using a balloon until 1.5 mm. Five days later, MAG3 renal sequential scintigraphy resulted in minimal function of the affected kidney. The follow-up color Doppler (CD-US), within 13 days, revealed the right renal artery of a regular caliber at this time (1.5 mm) in particular nearby the origin and in its first tract (the therapeutic angioplasty was practiced just here) (Fig. 7). The right kidney was highly increased in volume (right long axis R: 63.4 mm) with vascular signals distributed overall the parenchima to the outer portion of the subcortex (Fig. 8). The detection of the resistive index gave values within normal limits (RI 0.62) as well as the acceleration gradient: no more evidence of “parvus et tardus” waveform (Fig. 9). On the left side, qualitative and quantitative vascular findings were optimal.



**Fig. 1 – B-MODE US renal arteries in comparative. (A) right renal artery (0.9 mm, arrow) vs (B) left renal artery (1.9 mm, arrow).**

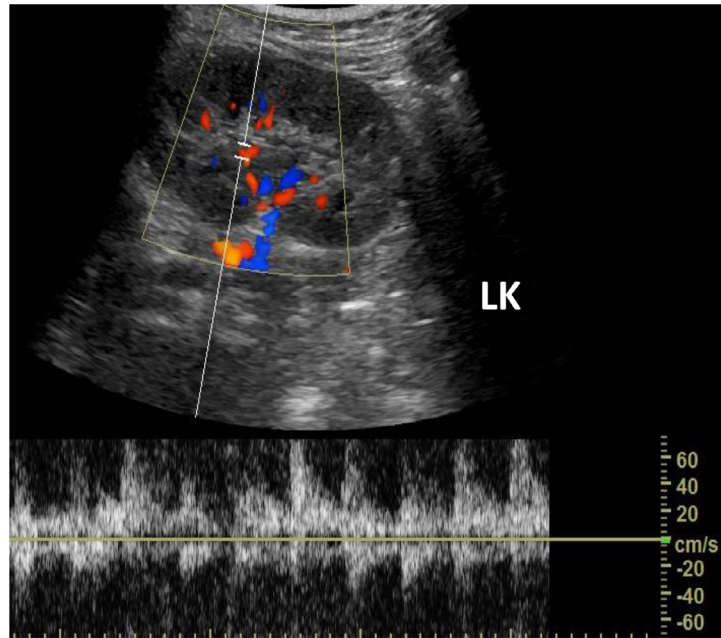


**Fig. 2 – Color-Doppler US (CD-US) of right kidney interlobar arteries: a significantly lower than the norm resistive index (RI 0.45) and an increased acceleration time. A “parvus and tardus” pulsus waveform.**

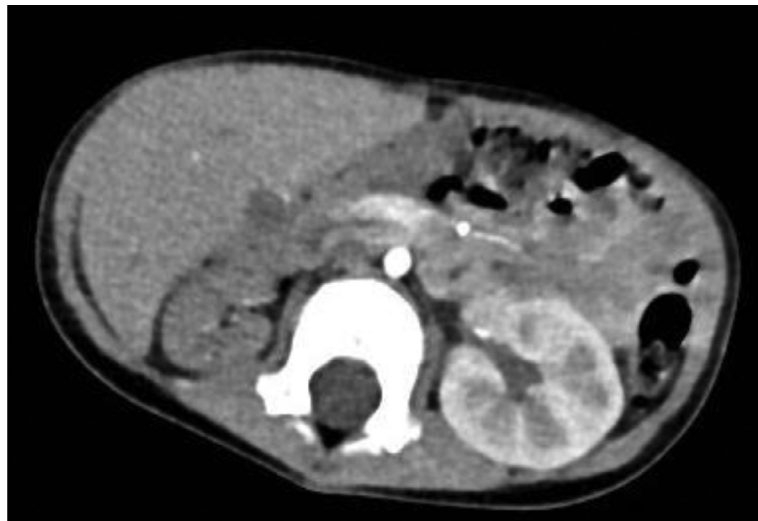
## Discussion

Pediatric RVH is a complex disorder that can be caused by various conditions [1,6]: mid aortic syndrome (aortic coarctation), aortic interruption, Ask-Upmark kidney (a renal segmental congenital hypoplasia associated with malignant hypertension), congenital anomalies of kidney and urinary tract, renal artery abnormalities such as developmental arterial dysplasia inflammatory arteritis (Takayasu arteritis, Kawasaki disease, and polyarteritis nodosa), extrinsic compression of the renal arteries due to a retroperitoneal mass (pheochromocytoma, neuroblastoma, adrenocortical neoplasm, Wilms tumor, RCC,

others), hematoma or other focal fluid collections, aneurysm or pseudoaneurysm, Neurofibromatosis type 1, Tuberous sclerosis, Marfan syndrome, Williams syndrome (idiopathic infantile hypercalciuria), radiation therapy, post-transplant thrombosis, and stenosis of the renal artery. First of all, RAS represents the most common trigger. It accounts for approximately 5%-10% [7] of secondary RVH in the pediatric population. It is often asymptomatic, but severe yet asymptomatic. RAS can occur as an isolated entity, or as a unilateral hypoplasia combined itself with stenosis, that is exactly our case. Hypoplasia, or long-segment developmental narrowing, is a rare cause of RVH [8,9] and it usually affects the lower thoracic or upper abdominal aorta (renal arteries), with a variable in



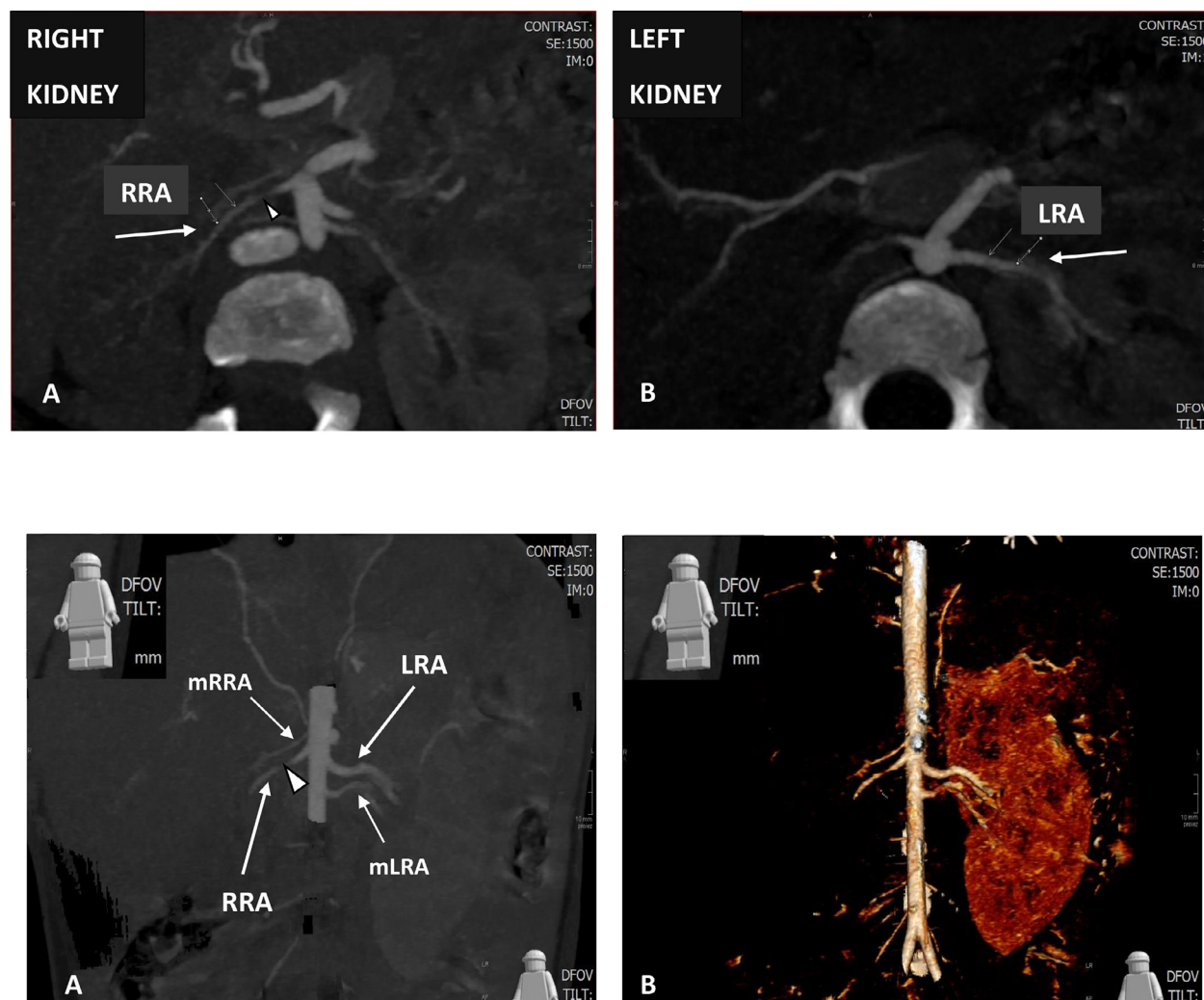
**Fig. 3 – Color-Doppler US (CD-US) of left kidney interlobar arteries: a resistive index within normal limits (RI 0.69). Absence of pulsus waveform alterations.**



**Fig. 4 – Axial computed tomography (CT) images (slice thickness 3 mm) of both kidneys. The right kidney is significantly decreased in size (right long axis R: 48 mm vs left long axis L:72 mm). A low enhancement was appreciated by the time of acquisition.**

length or degree and even collateral pathways. HHS is a malignant complication of RAS and/or renal artery hypoplasia. Nicholls [10] sustained that it is underdiagnosed and probably more common than previously thought. It can be clinically suspected when plasmatic levels of renin and aldosterone are high in values, in association with persisting vomiting, diarrhea, hyponatremia, hypokalemic hypochloremic metabolic alkalosis, nephrotic range proteinuria, polyuria, polydipsia, dehydration, and weight loss. Hypercalciuria and glycosuria have been less frequently reported. In particular, hypertension

remains refractory despite aggressive antihypertensive therapy. Laboratory findings of elevated plasma levels of renin in most cases suggest that the stimulation of renin release from the ischemic kidney plays an important role. The underlying pathophysiological mechanism consists in activation of the renin-angiotensin system caused by a reduced blood flow to—a part or all—one or both kidneys: it results in vasoconstriction and sodium/fluid retention induced by aldosterone leading to increased blood pressure, eventually. HHS is a diagnostic and therapeutic challenge in children. Imaging is cru-



**Fig. 5 – A-B, 6 A-B:** Three-dimensional CT reconstruction of the renal arteries / volume multiplanar MPR reconstructions, axial and coronal images. Arrows **RRA**: right renal artery; **LRA**: left renal artery; **mRRA**: multiple right renal artery; **mLRA**: multiple left renal artery. Arrowhead stenosis in RRA at about 6 mm from abdominal aorta diramation for a maximum extension of approximately 4 mm. **RRA** a right renal artery with a caliber half than the contralateral (1 mm vs 2.1 mm). Arrowhead a stenotic tract at about 6 mm from abdominal aorta diramation for a maximum extension of approximately 4 mm. **mRRA** a right filiform accessory renal artery, originating just above the main vessel. **LRA** a left renal artery, homogeneous along the whole course. **mLRA** a left accessory renal arter with a smaller caliber and a caudal emergence in relation to the main artery. **N.B.:** the right kidney had no enhancement when the left kidney was completely represented.

cial in confirming the early diagnosis and in the planning of an optimal treatment [5,6,11–14]. It is important for the potential resolution of hypertension and the recovery of renal function after renal revascularization, since interventional treatment may improve or cure hypertension and preserve renal function [15]. Moreover, reevaluation in time of the working diagnosis can be necessary to optimize the outcome [16]. When performed by experienced sonographers, US is the first choice tool in RVH screening [17] especially in children due to its non-invasiveness, repeatedly, and widespread availability. It does not use ionizing radiation and/or contrast agents as well as not require sedation. Moreover, pediatric population usually has a more suitable body habitus to US investigation thanks to a less abdominal and perivisceral fat tissue. If catecholamines

are elevated, CT is the initial test [18]. If no etiology is identified from these non-invasive studies, then DSA is mandatory [13,14,19]. US gray scale shows asymmetric features such as hyperechogenicity of the contralateral kidney, aberrant renal arteries and a narrowed vascular lumen of the main renal artery in a kidney otherwise normal in dimensions (indicative of a suspected accessory renal artery) [20,21]. Typical CD-US findings include an aliasing artifact (a bidirectional flow above and below the baseline), and localized perivascular tissue vibrations appearing as random color assignment in the parenchyma adjacent to the stenosis. But direct scanning of renal artery is often time-consuming and may be prevented by limiting factors such as bowel gas interposition, respiratory motion, an inappropriate insonation angle (not less

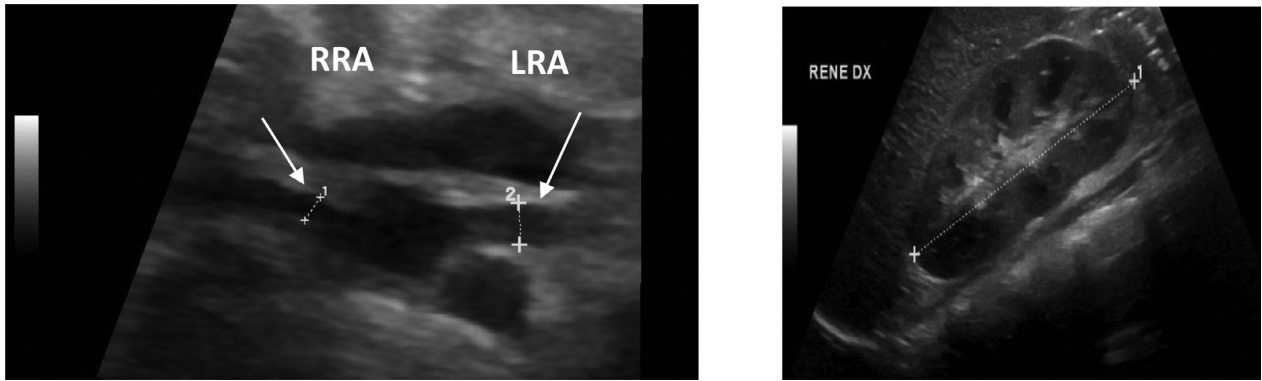


Fig. 7 – Follow-up B-MODE US post-angioplasty: renal arteries calibers in comparative. RRA: a regular caliber (1.5 mm) nearby the emergence and in its first tract with a rescued length of the right kidney (63.4 mm), at this time.

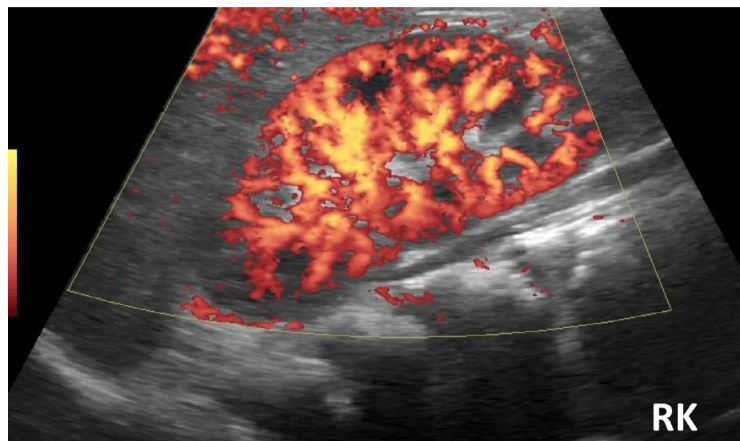


Fig. 8 – Follow-up color-Doppler US (CD-US) post-angioplasty: a great vascularization in the right kidney, overall the parenchyma to the outer portion of the subcortex.

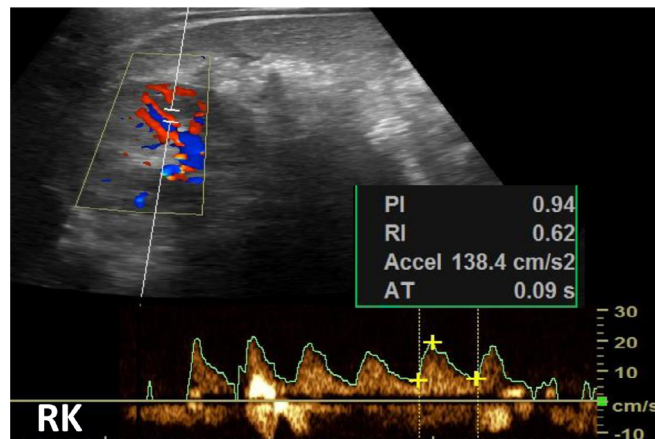


Fig. 9 – Follow-up color-Doppler US (CD-US) post-angioplasty: a resistive index value within the normal limits (RI 0.62) as well as the acceleration gradient. No more evidence of “parvus and tardus” pulsus waveform.

or equal to 60 degrees) or anatomical variants, for example, accessory renal arteries as well as a pediatric patient not completely compliant makes the Doppler evaluation really difficult [20,21]. Pitfalls and sources of error of CD-US can be corrected with proper scanning and interpretation [22]. Multiple renal arteries and intrarenal segmental stenosis can result in false negative Doppler [23]. CD-US is not very sensitive for detecting stenosis in accessory arteries or in small branch vessels [24]. To minimize the possibility of overlooking RAS in an accessory renal artery or segmental branch, spectral analysis should sample multiple regions including upper pole, mid pole and lower pole in each kidney. Five Doppler parameters, including renal peak systolic velocities (RPSVs) in the renal and interlobar arteries, renal-aortic ratio, renal-renal ratio, renal-segmental ratio and renal-interlobar ratio were measured throughout 2 types of approach: a direct evaluation of the renal artery at the level of the stenosis (direct or proximal parameters) or an indirect evaluation of the intrarenal vessels distal to the site of stenosis (indirect or distal parameters). A combination of intra and extra-renal flow parameters increases the sensitivity and specificity of the US analysis [25,26]. A peak systolic velocity (PSV) higher than 180 cm/s suggests a hemodynamically significant lesion (stenosis  $\geq 60\%$ ). Renal-aortic ratio, that is, the comparison of PSV values obtained in the prerenal abdominal aorta with those measured in the RAs, is more reliable than PSV because hypertension can cause increased PSV velocities in all the vessels in hypertensive patients. A RAR greater than 3-3.5 is pathological. Renal-segmental ratio, that is, a ratio of PSV measured in the renal artery to that obtained in the segmental artery, was the best parameter for Soares et al. [27]. Chain et al. [28] proposed to use renal renal ratio, that is, the rate between renal artery peak systolic velocity (RPSV) at the proximal or mid segment of the RA and RPSV measured at the distal segment of the renal artery because of the increased blood flow velocity through the stenosis, the immediate post stenotic segments and the decrease in blood flow velocity distal to the stenosis proportional to the degree of stenosis. The hemodynamic changes in downstream arterial vessels reflect the attenuated blood flow through the narrowed vessel during the ventricular systole, resulting in an abnormal “parvus et tardus” waveform [29]. It is characterized by a dampened and rounded systolic peak (parvus, ie, small and weak) and a delayed or prolonged early systolic acceleration (tardus, ie, late and delayed). It may be seen unilaterally, distal to a severe RAS, or bilaterally in mid-aortic syndrome (MAS) or coarctation [30 + pediatric imaging 1 da ricontrolare]. Above all, loss of ESP (early systolic peak) enables the identification of RAS with 95% sensitivity, 97% specificity, a 92% positive predictive value, a 98% negative predictive value [29]. Furthermore, distal quantitative criteria have been proposed: resistive indexes (RI), acceleration time (AT), and acceleration index (AI). A decreased RI value, less than 0.56, or a difference in RI between both kidneys  $>5\%$  (unilateral stenosis) are considered significant [28]. The resistive index (RI) value at CD-US may be very useful for predicting the response to revascularization [30]. If  $AT > 0.07$  s and  $AI < 3.0$  m/sec<sup>2</sup>, a high probability of a hemodynamically significant stenosis exists [25]. CT allows to objectify the findings already diagnosed on CD-US, in addition to 3D reformatting options that improve the analysis of angiographic findings. 3D volume rendering

gives an excellent representation of 3-dimensional anatomical relationships while maximum intensity projection (MIP) ensures the visualization until smaller accessory or segmental renal arteries (first and second order branches), with a greater sensitivity than US [11,18,31,32]. Images are acquired with thin collimation and bolus tracking on the abdominal aorta. Contrast-enhanced slices show delayed nephrographic progression in the affected kidney without perinephric manifestations. Sensitivity and specificity reported are very high in values, between 90% and 99%. Other CT advantages are fewer motion-related artifacts and no need for sedation or general anesthesia. CT should be performed immediately after US and just before DSA for the therapeutic planning. But it has a limitation about intraparenchymal branches beyond the third order; these last branches become visible with DSA, obviously. The higher price of CT is the exposure of the little patient to ionizing radiation, although very low-dose radiation protocols are used in children with fast scan acquisition. Therefore, in a suspected RVH in the pediatric age, the combination of US followed by CT should be used as a reliable and non-invasive work-up to diagnose or rule out a hemodynamically significant—isolated or combined with hypoplasia—unilateral RAS, to confirm then with DSA that remains the gold standard to diagnose RVH [14,15,19,33]. It is recommended when clinical and laboratory criteria are highly suggestive of renovascular disease, even when radiological non-invasive methods are normal and can be combined with percutaneous transluminal angioplasty PTA/stenting if medical treatment is obsolete. Primarily because of its excellent spatial and contrast resolution, DSA has the advantage of a concomitant treatment of different lesions as part of the same procedure, but we must remember its invasive nature due to vascular complications including arterial dissection, thrombosis, embolic phenomenon, delayed pseudoaneurysm, perforation, and an increased frequency of stroke in children with concomitant cerebrovascular disease [34]. Over 40% of renal artery angioplasty would develop restenosis [35]. Uncontrolled hypertension itself could cause irreversible remodeling of vascular endothelium, resulting in permanent hypertension. But HHS, caused by isolated or combined with hypoplasia unilateral RAS, is a reversible disease. Angioplasty is technically successful and can improve renal function in addition to improving hypertension. The diagnostic (vs our-case therapeutic) role of DSA is limited to situations of mismatch between the 2 previous methods (US and CT) or unexplained hypertension in patients with negative imaging. Stenting is only used when angioplasty fails. Ethanol embolization may be appropriate in children with untreatable focal renin-producing areas. Surgical procedure is reserved for exceptional situations. In all instances, a multidisciplinary team approach by pediatric nephrologists, pediatric vascular surgeons, pediatric radiologists, and pediatric interventional radiologists should be used to provide optimal care and life expectancy in children.

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## Conclusions

Although HHS is a rare entity, it should be suspected in little patients with unresponsive hypertension and associated

signs and symptoms. Imaging step-by-step is crucial to lead an early diagnosis and guide the optimal multidisciplinary management.

### Patient consent

According to guidelines of the *Radiology Case Reports Journal*, “formal consents are not required for the use of entirely anonymized images from which the individual cannot be identified for example, X-rays, ultrasound images, pathology slides or laparoscopic images, provided that these do not contain any identifying marks and are not accompanied by text that might identify the individual concerned.”

Informed consent was obtained by both the parents of the patient for publication of this case.

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