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Case report

Renal artery fibromuscular dysplasia: diagnostic challenges in a child presenting with hyponatremic hypertensive syndrome (HHS)

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Abstract

A 2-year-9-month-old boy presented with renovascular hypertension caused by middle-segment stenosis of the right renal artery, and a severe hypertensive crisis, accompanied by hyponatremia, hypokalemia, and transient proteinuria. Fibromuscular dysplasia (FMD) is the most common cause of renovascular disease in children. However, the diagnosis of FMD is often delayed because findings on renal sonograms with Doppler are frequently missed. A high index of suspicion is required to further investigate a renovascular cause when persistent hypertension in a child cannot be otherwise explained. We present the challenges of reaching a diagnosis in a resource-limited setting and discuss how a multidisciplinary approach was key to successfully manage a young child with renovascular disease.

Keywords

Fibromuscular dysplasia, renovascular disease, hyponatremic hypertensive syndrome, renal artery stenosis, childhood hypertension.

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Introduction

The incidence of hypertension in children has increased in recent years but is frequently undiagnosed in the pediatric population [1, 2]. While primary hypertension is more common in adults, secondary hypertension is predominantly found in children. Among secondary causes, renal and renovascular diseases are some of the most identifiable. Renovascular disease alone accounts for up to 10% of hypertensive cases in children and is of significant clinical importance due to its amenability to intervention [3]. Unfortunately, identifying renovascular disease is diagnostically challenging, as 62% of children are clinically asymptomatic at presentation [4]. Although a presentation involving a hypertensive emergency is rare, it has been described in a few cases of hyponatremic hypertensive syndrome (HHS) in children related to fibromuscular dysplasia (FMD) or renal thrombosis [4]. Non-invasive imaging techniques in young children are challenging due to the small size of the arteries and the child's willingness to undergo such procedures. Doppler ultrasonography (USG), computed tomography (CT) angiography (CTA), and magnetic resonance angiography (MRA) can all be helpful. However, none have sufficiently high sensitivity to detect FMD in a child with clinical suspicion [5]. We report a case that illustrates these diagnostic difficulties, particularly in the context of an uncommon presentation.

Case summary

A 2-year-9-month-old boy presented to the Emergency Department with a history of vomiting for 1 week, occurring 3-4 times a day. The vomiting was non-projectile, non-bilious, and not associated with meals. Upon admission to the ward, he experienced an episode of generalized tonic-clonic seizure lasting for 10-15 minutes. This was his first-ever seizure episode, and there was no family history of epilepsy or kidney disease. There was no history of previous urinary tract infections.

His physical examination revealed extremely high blood pressure (BP) of 188/160 mmHg (> 99th percentile). His height and weight were at the 50th percentile, and his BMI was 15.51 kg/m^2. Apart from bilateral lower limb hyperreflexia, his neurological examinations, including his fundoscopy, were normal. His abdominal examination showed no hepatosplenomegaly or any ballotable mass, and no evidence of renal bruit.

The seizure was aborted with a dose of suppository diazepam. He remained severely hypertensive and required intravenous (IV) labetalol infusion over 4 days before transitioning to oral antihypertensive agents. He was also treated with IV antibiotics for presumed meningitis. An urgent CT scan of the brain showed no evidence of cerebral edema or intracranial bleeding. Despite the gradual improvement in his hypertension, he quickly recovered following his seizure episode, with no visual complaints, headaches, or altered mental state.

Blood investigations showed normal total white cell count and CRP, with values of 6.1 x 10^9 g/dL and < 5 mmol/L, respectively. His electrolytes showed a low sodium level of 123 mmol/L and a low potassium level of 2.6 mmol/L. His renal functions remained normal. He had proteinuria of 3+, and red blood cells were negative. His C3 (1.35 g/L), C4 (0.48 g/L) and ANA were normal. Supine serum renin and aldosterone were raised with 4.64 µg/L/hr (normal reference 0.6 to 4.3 µg/L/hr) and 913.7 pmol/L (normal reference 99.8 to 282.9 pmol/L), respectively.

The renal USG and Doppler were normal, and kidney sizes were appropriate for his age. There was no Doppler evidence of renal artery stenosis (RAS) (**Fig. 1**). Upon discharge, his DMSA scan revealed scarring of the upper pole of the right kidney (**Fig. 2**), and he showed evidence of left-eye hypertensive retinopathy.

He remained hypertensive despite being on triple antihypertensive agents. An MRA conducted 6 months later revealed the presence of an irregular and beaded appearance in the middle segment of the right renal artery, suggestive of

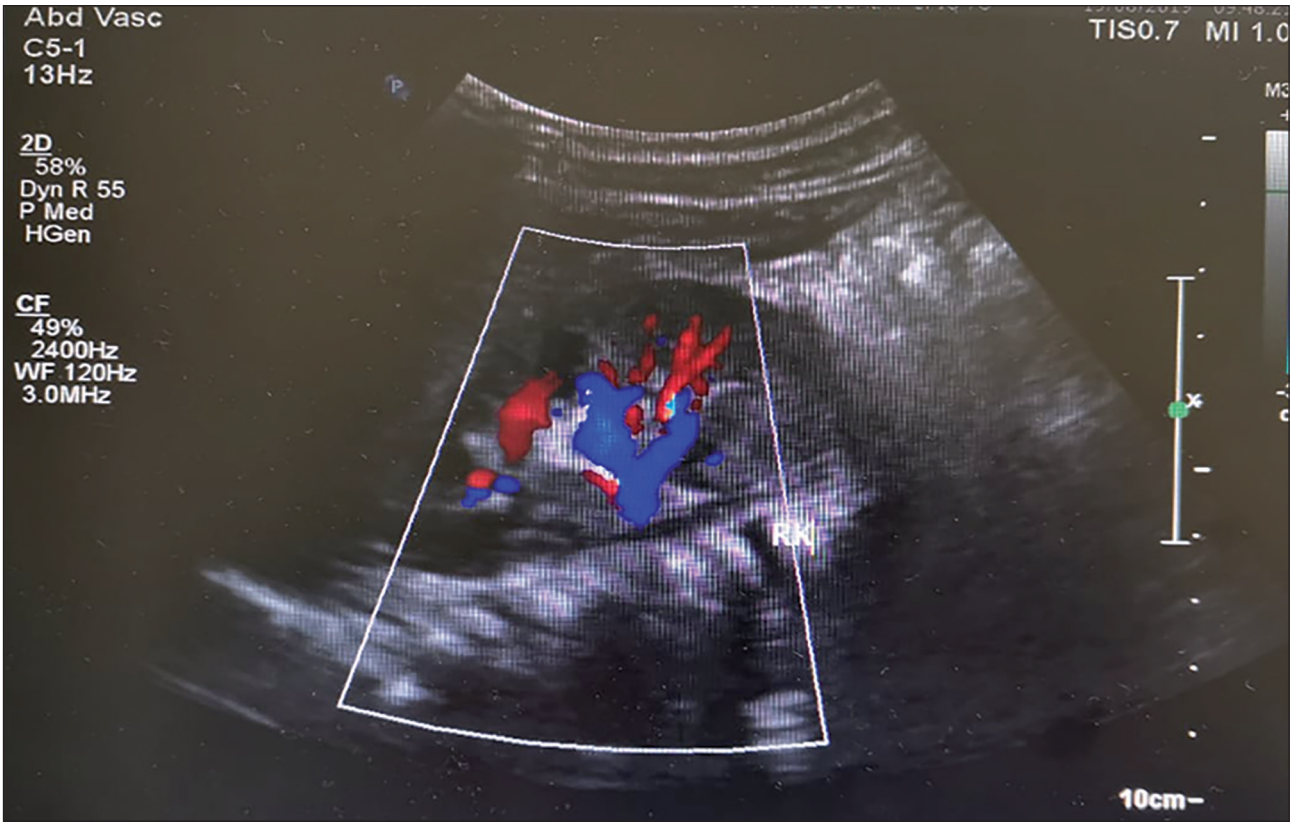

Figure 1. On Doppler evaluation, the resistant index in both kidneys was 0.69 to 0.70, which was within normal limits.

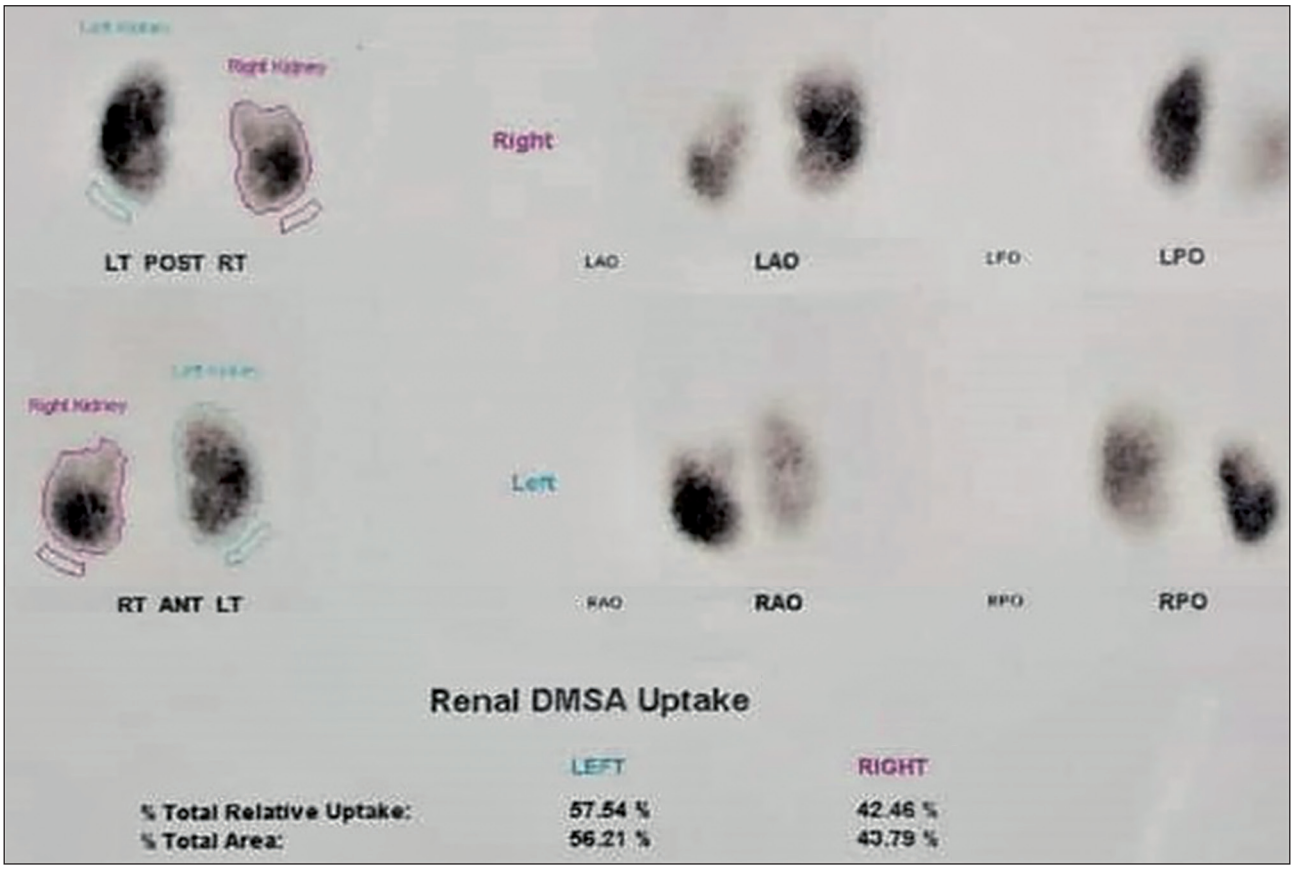

Figure 2. Both kidneys are normal in position. There is cortical uptake defect in the upper pole of the right kidney. There is homogenous accumulation of tracer in the left kidney. The right kidney contributes 42% and the left 58% of the total functioning parenchymal mass.

FMD. There was no evidence of pre- or post-stenotic dilatation seen on the MRA. However, a renal angiogram (**Fig. 3**) revealed tight stenosis (70% stenosis) of the right superior segmental artery, with post-stenotic dilatation and multiple dilated distal branches and stenotic segments suggestive of FMD.

He underwent right renal angioplasty 2 years after his first presentation, and post-angioplasty results showed a reduction of stenosis from 70% to 30% (**Fig. 4**). His BP improved following the procedure, but he remained on 2 antihypertensive medications at the 3-month follow-up. He will continue to receive close monitoring. His ECHO did not reveal any left ventricular hypertrophy. Since his hospital discharge, however, he has remained seizure-free with no neurological sequelae.

Discussion

Secondary hypertension in children often has an underlying, potentially curable aetiology. About 85% of children with hypertension have a known secondary cause, the most common of which is renal parenchymal disease [6]. Hypertension in children is more likely due to a secondary cause if the BP exceeds the age-sex-height-specific 99th percentile + 5 mmHg (stage 2 hypertension) or if the child is young at presentation [7]. Therefore, an age-based approach is commonly employed in diagnosing hypertension in these children. **Tab. 1** highlights the differential diagnoses of secondary hypertension causes in children, their estimated prevalence and age of onset.

For younger children, investigations are primarily directed toward more common causes, such as glomerulonephritis and urinary tract anomalies. However, these are not absolutes; it is essential to bear in mind the possibility of overlapping causes between age groups, as illustrated in this case. Following the exclusion of renal parenchymal disease and urinary tract anomalies, renovascular disease remains a challenging diagnosis. FMD is the most common cause of RAS in children, although its actual prevalence is still unknown.

FMD, or fibromuscular hyperplasia, is a non-atherosclerotic, non-inflammatory vascular disease that primarily affects medium-sized and small arteries, most commonly the renal, abdominal aorta, and mesenteric arteries. The aetiology of FMD in children remains unknown. There are 3 different types of FMD based on histological classification: intimal fibroplasia, medial fibroplasia, and peri-arterial or periadventitial fibroplasia [8]. These findings have a good correlation with radiological appearances.

One study showed that the mean age for diagnosing FMD in children is 7 years, and those diagnosed earlier are often associated with underlying diseases or syndromes. FMD may be linked to conditions such as Williams syndrome, Alagille syndrome, neurofibromatosis type 1, and

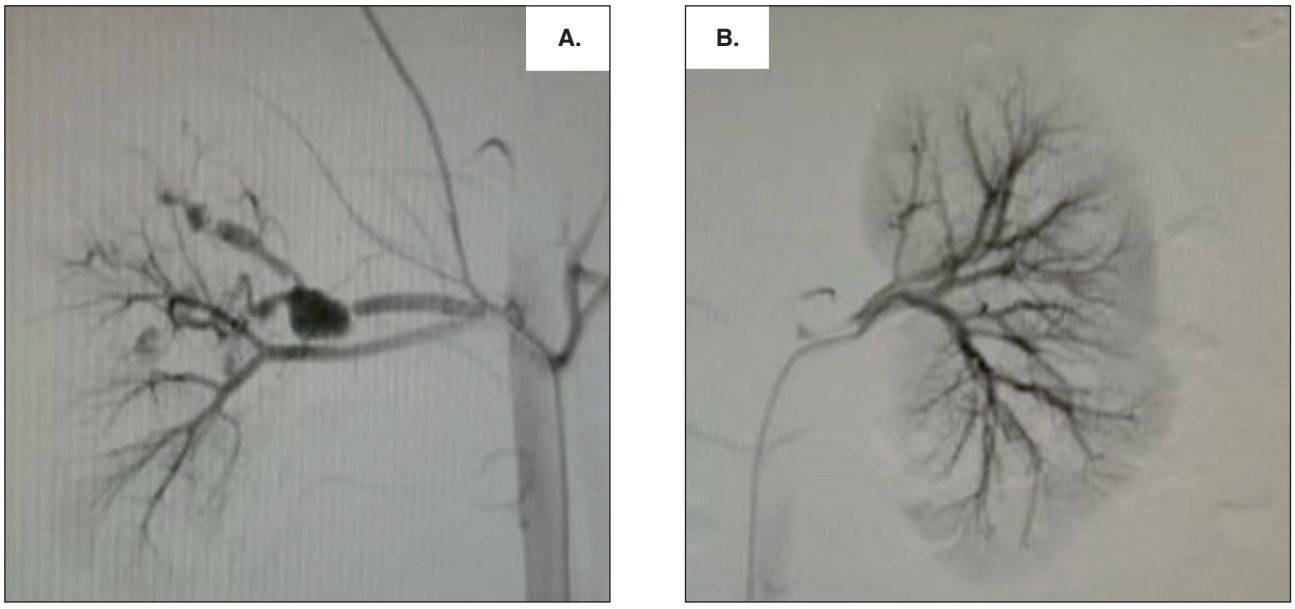

Figure 3. There is a tight stenosis in the right superior pole renal artery with post stenotic dilatation. The branches distal to this dilatation are also ectatic, with multiple dilated end stenotic segments.The right inferior pole renal artery and the left renal artery and its branches are normal. **A.** Right. **B.** Left.

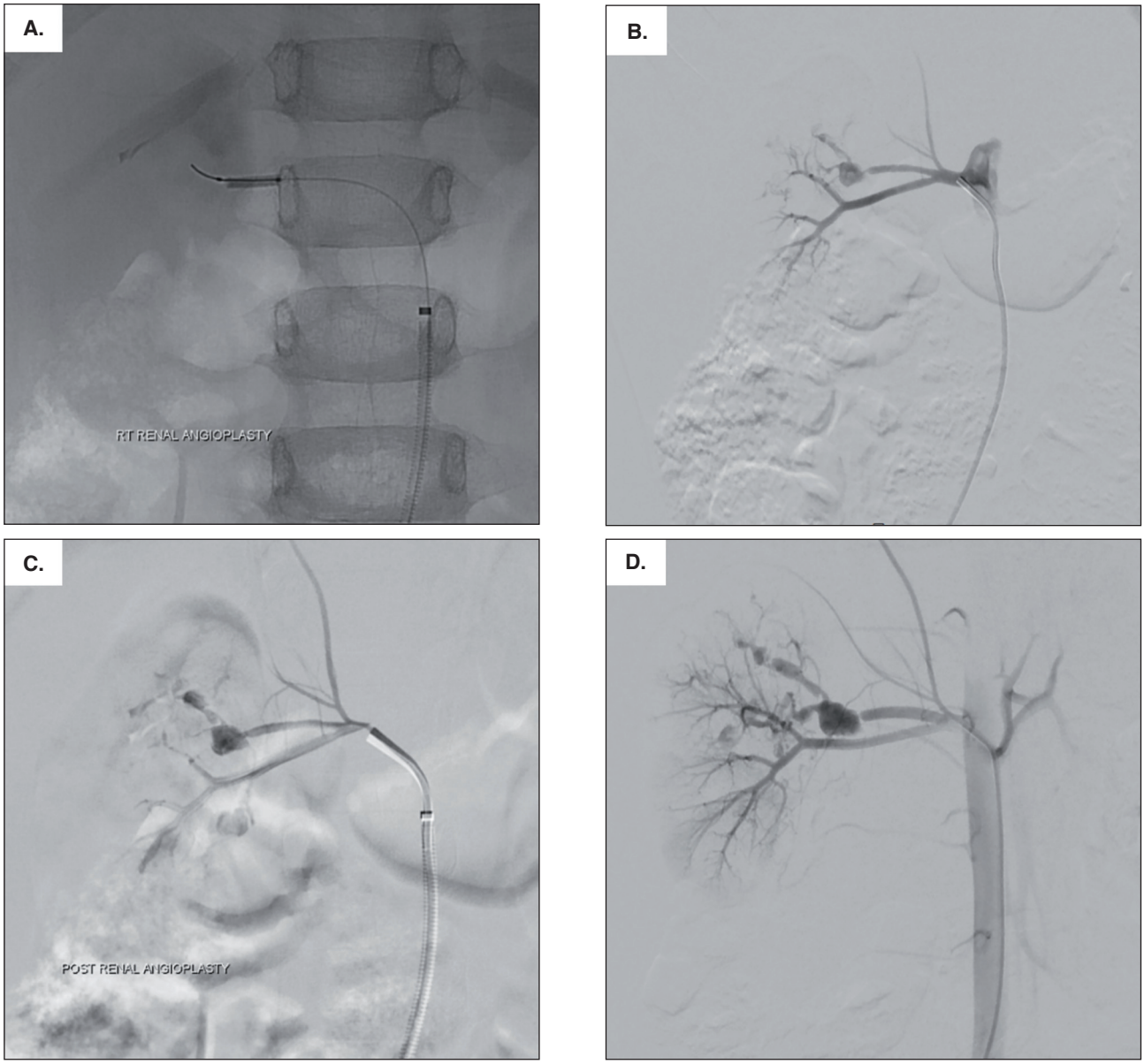

Figure 4. Beaded appearance of the right upper pole segmental renal artery with focal narrowing seen at the distal right upper pole artery. A microwire and microcatheter were inserted beyond the stenotic segment (**A** and **B**). This was followed by an insertion of an angioplasty balloon inflated to nominal pressure. Post angioplasty showed a reduction in stenosis from 70% to 30% (**C** and **D**).

Table 1. Causes of secondary hypertension in children (compiled from UpToDate® [9]).

Category	Aetiology	Estimated prevalence	Age of onset
Renal parenchymal disease	Glomerulonephritis	0.5-2.5 in 100,000	6-15 years old
	Renal scarring from congenital anomaly of urinary tract	10-15% of recurrent urinary tract infections lead to scarring	Variable
	Polycystic kidney disease	1 in 20,000	1-20 years old
Renovascular disease	FMD	Unknown	6-10 years old
	Takayasu arteritis	Unknown	12 years
	Neurofibromatosis type 1	1 in 4,560	3 months-15 years old
Endocrine disease	Phaechromocytoma	0.1 in 100,000	6-14 years old
	Neuroblastoma	1 in 7,000	1-2 years old
	Cushing syndrome	2-5 in 1,000,000	> 6 years old
Cardiac disease	Coarctation of aorta	4 in 10,000	Early infancy
Drugs	Glucocorticoid	Variable	Variable
	Arsenic poisoning	Variable	Variable
	Cyclosporin/Tacrolimus	Variable	Variable

FMD: fibromuscular dysplasia.

connective tissue disorders, including Ehlers-Danlos syndrome and alpha-1 antitrypsin deficiency [10]. In another study, family history was significant; 17.2% of pediatric FMD patients reported a diagnosis of FMD in a first- or second-degree relative, compared to 4.7% of adult patients [11]. Our patient did not exhibit any clinical features or have a family history of genetic or connective tissue disorders. Unlike in adults, FMD in children does not show any sex predilection.

The clinical features of FMD depend on the extent and severity of arterial stenosis, which in turn affects the degree of renal perfusion. Consequently, the kidney releases a high amount of the renin hormone, activating the angiotensin system and inadvertently leading to hypertension. As hypertension is often the sole presenting sign, more than half of the children with FMD are asymptomatic and are only detected as incidental findings during routine physical examinations. Among those who are symptomatic, headaches, dizziness, and abdominal pain are common features. In our patient, the presentation of vomiting, seizures, high BP, and electrolyte imbalance warranted a more extensive diagnostic approach before concluding a diagnosis of FMD. The presence of renal bruit is pathognomonic for RAS; however, its absence does not exclude FMD.

Various opinions exist regarding the optimal diagnostic strategy for RAS; factors such as the patient's age, need for sedation, the likelihood of renovascular disease, and the use of contrast and radiation must all be considered.

Renal USG and Doppler remain the first choices as they are non-invasive, less time-consuming, and easily available. All children with confirmed hypertension should undergo renal ultrasound evaluation, regardless of age. However, this approach is highly operator-dependent, and patients may require subsequent arteriography. A study suggested that experienced operators using multiple USG views could reliably identify children with FMD and avoid false-negative or false-positive results [12]. Nonetheless, many cases may still be missed, as Doppler studies can detect only stenotic lesions when severe.

MRA and CTA provide better arteriography, and studies in adults and case reports in children have shown better sensitivities compared to sonographic imaging. A study by Louis et al. concluded that Doppler USG was significantly less sensitive (28%), while MRA and CTA had better sensitivities (62.5% and 84.2%, respectively) [13].

However, catheter-based angiography remains the imaging modality of choice in children due to smaller main renal artery vessels. The degree of stenosis and pre- and post-stenotic dilatation evidence are better appreciated on renal angiograms than MRA or CTA.

Therefore, despite its invasiveness, renal angiography remains the gold standard for diagnosing FMD and is recommended in all cases with strong suspicion of the condition. The most common angiographic appearance in patients with FMD is an artery resembling a string of beads, indicating multifocal involvement. In the renal and internal carotid arteries, this typically occurs in the mid and distal portions, contrasting with atherosclerosis, which commonly occurs at the origin or proximal portion of the artery.

Regarding clinical presentation, our patient's symptoms align with the definition of HHS. The combination of hypokalemia, hyponatremic hypovolemia, and hypertension in a child with suspected renovascular disease is a useful clue for HHS. This is further supported by elevated renin and aldosterone levels. The mechanism of hyponatremia in HHS is thought to result from both diuresis and natriuresis in response to hypertension and elevated ADH levels, leading to water conservation and volume depletion. Severe hyponatremia can cause cerebral edema and, if uncorrected, may lead to uncontrolled seizures.

Another condition that frequently accompanies HHS is posterior reversible encephalopathy syndrome (PRES). This potentially reversible neurological condition often affects the posterior regions of the brain. PRES is well-recognized in adults but is increasingly reported in children with secondary hypertension. Clinical features include seizures, altered mental consciousness, visual impairment, vomiting, and both focal and generalized neurological defects. Typical MRI findings for PRES show hyperintensities on T2-weighted MRI and fluid-attenuated inversion recovery (FLAIR) imaging, accompanied by increased apparent diffusion coefficient (ADC) values.

The treatment of both HHS and PRES primarily involves supportive care, including adequate seizure control, BP management, fluid replacement, and treatment of the underlying disease. Antihypertensive medications of choice are calcium channel inhibitors and beta blockers. Prognosis is generally favorable if detected early. However, in a series by Covarrubias et al., 6 had a fatal outcome

out of 22 patients with PRES of various etiologies, while a significant number experienced permanent neurological sequelae [14].

While nearly all children with FMD will be treated with anti-hypertensives, a few will require definitive therapy involving revascularization of the affected renal arteries. Balloon angioplasty is the preferred initial surgical intervention, as it is safe and has shown good outcomes in BP improvement. Stent placement is generally avoided due to the small vessel size, which complicates its placement and increases the risk of endothelial injury. Rarely, surgical bypass may be required for severely stenotic segments. Despite revascularization efforts, complete resolution of hypertension without the aid of anti-hypertensive medications is achieved in only 30-50% of patients [15].

Conclusion

FMD is a rare renovascular disease that affects children and can lead to long-term morbidity. It requires a high index of suspicion for diagnosis. Children who present with hypertension, accompanied by HHS and supported by elevated renin levels, should alert physicians. As illustrated in our case report, renal angiography remains the gold standard for diagnosis, as ultrasound and advanced imaging techniques such as MRA and CTA scans have a relatively high false-negative rate, especially in cases involving small-vessel disease. Balloon angioplasty has been shown to improve BP control; however, many children undergoing this treatment remain hypertensive and require close follow-up.

Informed consent

Informed consent was obtained from the patient's guardian for this case report publication and any accompanying images.

Declaration of interest

The Authors have no conflict of interest to declare. This report did not receive any funds or grants for its publication from any known source, either public or commercial sectors.

References

1. Rumman RK, Matsuda-Abedini M, Langlois V, Radhakrishnan S, Lorenzo AJ, Amaral J, Mertens L, Parekh RS. Management and outcomes of childhood renal artery stenosis and middle aortic syndrome. Am J Hypertens. 2018;31(6):687-95.
2. Peco-Antic A. Pediatric hyponatremic hypertensive syndrome. Therapy. 2005;2(2):301-9.
3. Tullus K. Renal artery stenosis: is angiography still the gold standard? Pediatr Nephrol. 2011;26:833-7.
4. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. JAMA. 2007;298:874.
5. Brun P, Kchouk H, Mouchet B, Baudouin V, Raynaud A, Loirat C, Azancot-Benisty A. Value of Doppler ultrasound for the diagnosis of renal artery stenosis in children. Pediatr Nephrol. 1997;11:27-30.
6. Arar MY, Hogg RJ, Arant BS Jr, Seikaly MG. Etiology of sustained hypertension in children in the southwestern United States. Pediatr Nephrol. 1994;8(2):186-9.
7. Parikh P, Duhame D, Monahan L, Woroniecki R. Renal artery stenosis precipitates hyponatremic hypertensive syndrome and posterior reversible leukoencephalopathy. Front Pediatrics. 2015;3:40.
8. Luscher TF, Lie JT, Stanson AW, Houser OW, Hollier LH, Sheps SG. Arterial fibromuscular dysplasia. Mayo Clin Proc. 1987;62:931-2.
9. https://www.wolterskluwer.com/en/solutions/uptodate, last access: June 2022.
10. Schievink WI, Meyer FB, Parisi JE, Wijdicks EF. Fibromuscular dysplasia of the internal carotid artery associated with alpha-1 antitrypsin deficiency. Neurosurgery. 1998;43:229-33.
11. Green R, Gu X, Kline-Rogers E, Froehlich J, Mace P, Gray B, Katzen B, Olin J, Gornik HL, Cahill AM, Meyers KE. Differences between the pediatric and adult presentation of fibromuscular dysplasia: results from the US Registry. Pediatr Nephrol. 2015;31(4):641-50.
12. Tullus K, Roebuck DJ, McLaren CA, Marks SD. Imaging in the evaluation of renovascular disease. Pediatr Nephrol. 2010;25(6): 1049-56.
13. Louis R, Levy-Erez D, Cahill AM, Meyers KE. Imaging studies in pediatric fibromuscular dysplasia (FMD): a single-center experience. Pediatr Nephrol. 2018;33(9):1593-9.
14. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. Am J Neuroradiol. 2002;23:1038-48.
15. Trinquart L, Mounier-Vehier C, Sapoval M, Gagnon N, Plouin P-F. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension. 2010;56(3):525-32.