Pediatr Nephrol (2002) 17:524–526
DOI 10.1007/s00467-002-0882-6

CLINICAL NEPHROLOGY

**David Menschik · Harold Lovvorn · Ashley Hill
Patrick Kelly · Deborah P. Jones**

An unusual etiology of hypertension in a 5-year-old boy

Received: 25 September 2001 / Revised: 11 March 2002 / Accepted: 11 March 2002 / Published online: 25 May 2002

Abstract Ganglioneuromas are rare benign tumors of neural crest origin, arising from ganglia of the sympathetic nervous system and adrenal medulla. These masses are usually detected during the first 2 decades of life and are generally discovered incidentally. We present a 5-year-old boy with sickle β-thalassemia whose hypertension is caused by a perihilar ganglioneuroma encasing the right renal artery and distorting the right renal vein. The tumor was resected and the child's blood pressure subsequently normalized.

Keywords Hypertension · Ganglioneuroma · Renovascular hypertension · Sickle cell disease · Renal mass

Nearly 90% of definable hypertension in the 1st decade of life is attributable to diseases of the kidney and renovascular abnormalities [1, 2]. Other causes of pediatric hypertension include cardiovascular, endocrine, and central nervous system diseases, as well as drugs, stress, and pain.

In our patient, hypertension was initially ascribed to pain from a vaso-occlusive crisis as a result of sickle β-thalassemia. However, once his blood pressure remained elevated despite adequate analgesia, an extensive workup for hypertension ensued that resulted in the discovery of a perinephric ganglioneuroma.

A 5-year-old boy with sickle β-thalassemia presented to the Emergency Department of LeBonheur Children's Medical Center (LBCMC) complaining of severe pain in his right lower thigh through his knee. Blood pressure was 174/124 mmHg. The child had had one previous hospitalization at 4 years of age for a vaso-occlusive crisis. He had no other known complications of sickle cell disease. Previous BP readings performed in the Hematology Clinic from as recently as 10 months earlier were normal. Family history was remarkable for sickle cell disease, essential hypertension, and type 2 diabetes mellitus. He had recently received a 5-day course of prednisone (completed on the day of admission) and aerosolized albuterol for mild persistent asthma. In the Emergency Department, he received intravenous fluids, morphine and ketorolac with which pain was moderately improved. Despite the abatement of his pain, his blood pressure remained elevated. He had mild tachycardia, mild tachypnea, and a normal oxygen saturation level and was afebrile. He appeared to be in some discomfort but was in no acute distress. His right leg and thigh were tender to palpation. Femoral pulses were normal, and no abdominal bruit was noted. Skin examination revealed no café-au-lait spots. The remainder of his physical examination was unremarkable. Complete blood count, basic chemistry panel (which included a blood urea nitrogen level of 5 mg/dl and a serum creatinine level of 0.4 mg/dl) and urinalysis were all within normal limits.

The patient was admitted to LBCMC with a diagnosis of vaso-occlusive crisis. The ketorolac was discontinued the following day after which analgesia was provided by intravenous morphine via a patient-controlled pump. Due

D. Menschik · D.P. Jones (✉)
Department of Pediatrics,
University of Tennessee Center for Health Sciences, Memphis, TN, USA
e-mail: dpjones@utmem.edu
Tel.: +1-901-5725366, Fax: +1-901-5725036

H. Lovvorn
Department of Surgery,
University of Tennessee Center for Health Sciences, Memphis, TN, USA

A. Hill
Department of Pathology,
University of Tennessee Center for Health Sciences, Memphis, TN, USA

D. Menschik · H. Lovvorn · P. Kelly · D.P. Jones
LeBonheur Children's Medical Center, Memphis, TN 38103, USA

P. Kelly
Department of Hematology/Oncology,
St. Jude's Children's Research Hospital, Memphis, TN, USA

D.P. Jones
Children's Foundation Research Center, Memphis, TN, USA

D.P. Jones
50 North Dunlap, Room 301,
LeBonheur Children's Medical Center, Memphis, TN 38103, USA

to persistent BP elevation despite adequate analgesia, treatment was initiated with captopril (0.2 mg/kg q 8 h) and amlodipine (0.15 mg/kg/day). A renal ultrasound revealed increased echogenicity of both kidneys. Renal arteries and veins had normal waveforms by Doppler. An echocardiogram showed left ventricular and septal wall hypertrophy (7.5 mm and 7.9 mm thick respectively), but no coarctation or other abnormalities. On hospital day 4, the patient complained of increased pain in his right knee and thigh, and magnetic resonance imaging (MRI) of his lower extremities was performed. The kidneys were included in the study. The MRI revealed a right perinephric mass measuring 4.0×3.0×3.6 cm encasing the right renal artery (Fig. 1). A contrasted computed tomography (CT) study of his chest, abdomen and pelvis showed anterior displacement of the right renal vein and an area of infarction or ischemia of the inferior pole of the right kidney. No metastases were seen. Urine metanephrines and catecholamines were collected and found to be within normal limits. Serum aldosterone and renin concentrations returned within normal limits.

He was then referred to St. Jude's Children's Research Hospital (SJCRH) for further diagnostic studies. Bone marrow aspirates and biopsies showed no evidence of metastatic disease. A bone scan revealed no evidence of metastases. It was noted at the time of the bone scan that excretion of technetium-99 medronate from the right kidney was delayed. Magnetic resonance angiography (MRA) showed the right renal artery to be patent and equal in caliber to the left renal artery; however, marked anterior displacement of the right renal vein was noted. The following day, a gross total resection of the tumor was performed. The mass enveloped the right renal artery and its hilar branches. The anterior displacement of the right renal vein was confirmed. The main renal artery and its hilar branches were completely liberated of tumor. Pathologic examination demonstrated mature ganglion cells scattered throughout the tumor without neuroblasts, consistent with a mature ganglioneuroma. The adrenal medulla was uninvolved by the tumor, suggesting origination from the sympathetic chain. No regional metastatic foci were identified.

In the immediate postoperative period, the patient's blood pressure was normal without medication. Postoperative renal scans performed showed gradual return of normal function in the right kidney. A follow-up CT scan with contrast confirmed the resolution of the wedge-shaped infarction in the right posterior lower pole. BP readings off medication were 114/69 and 104/61 mmHg (95th percentile, 110/72 mmHg) at 2 and 3 months post operation.

Several possible etiologies exist as the source of hypertension in this child. Although pain can be a cause of transient hypertension and was the first explanation for hypertension in this child, hypertension during pain crises in sickle cell patients is rare. Sickle cell patients actually have lower than average blood pressures and do not become hypertensive in painful, vaso-occlusive crises [3].

It is unlikely that production of catecholamines by the tumor caused this child's hypertension since levels were not elevated in the urine. Of 59 children with neuroblastic tumors, 11 children (one of whom had a ganglioneuroma) had hypertension at diagnosis [4]. Ten of these 11 children had their urinary homovanillic acid (HVA) and vanillylmandelic acid (VMA) levels measured, and all had elevated levels of both metanephrines except one child whose

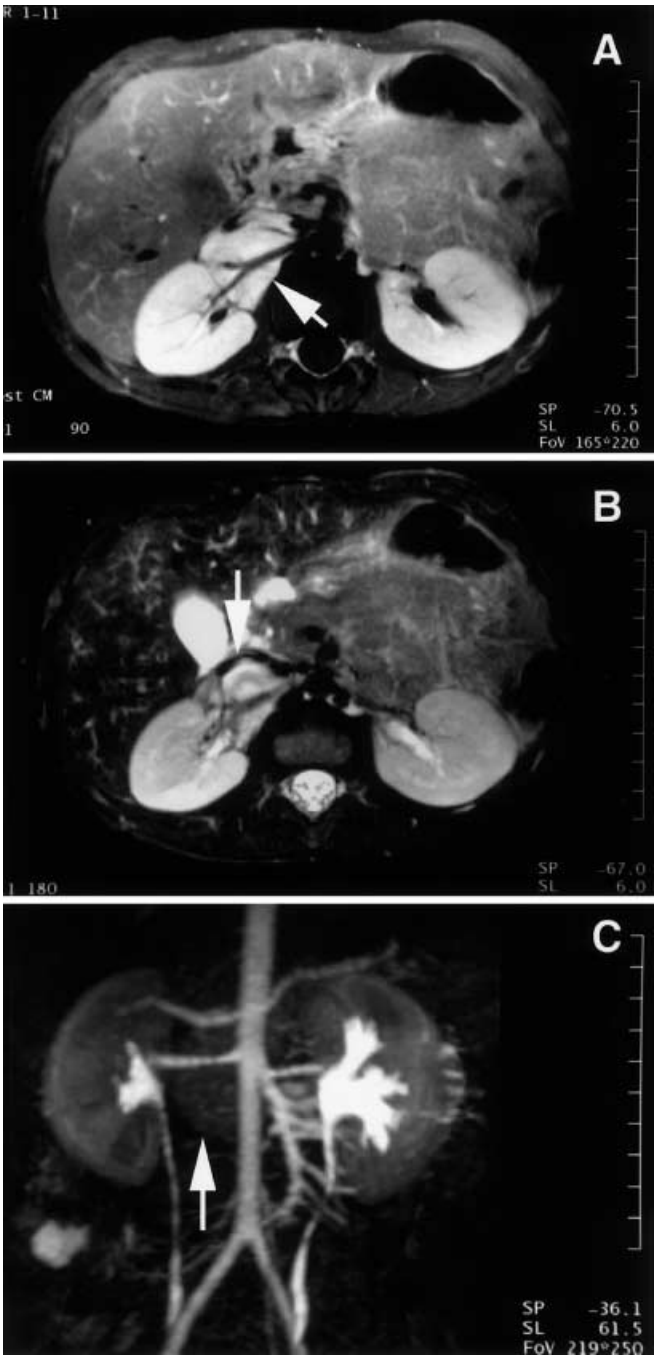

Fig. 1A–C Magnetic resonance imaging of the abdomen shows a right perinephric mass. **A** Axial view of mass (margin denoted by *arrow*) encasing right renal artery. **B** Axial view of mass depicting marked anterior displacement of right renal vein (*arrow*). **C** Magnetic resonance angiography of the abdomen in the coronal view showing a single right renal artery coursing through the mass (*arrow*). Hypoattenuation of lower pole of right kidney is consistent with ischemia or infarct

urinary HVA levels were normal and VMA levels were elevated [4]. In a separate series including 20 children, all with ganglioneuromas, only 4 (20%) had elevation of urinary VMA and/or HVA levels. The same study posited a direct correlation between tumor size and metanephrine levels and found that all ganglioneuromas in the study group under 200 cm^3 were associated with normal VMA and HVA levels [5]. Thus, it is not surprising that our patient's tumor, which measured less than 50 cm^3, did not produce elevated metanephrines in a 24-hr urine sample.

Renal parenchymal damage could have produced hypertension through activation of the renin-angiotensin-aldosterone cascade (RAAC). While nephropathy/glomerulonephritis can occur in sickle cell patients, this condition is unlikely to have been present in our child given the absence of proteinuria and hematuria. Alternatively, compression of the renal parenchyma by the mass, independent of renal artery or vein compromise, may have produced renal ischemia triggering the RAAC [6]. Such a mechanism is unlikely in our case given the absence of significant renal compression by the mass on imaging studies. More likely, renal parenchymal ischemia caused by either direct compression of renal vasculature (e.g., a branch of the renal artery) or overall diminished blood flow through the kidney secondary to renal vein distortion contributed to this child's hypertension.

A further attractive explanation for this child's hypertension is that the RAAC was triggered by anatomic constraints on the renal artery by the mass, despite normal peripheral renin levels and normal Doppler ultrasonography. Although renovascular hypertension in children is commonly associated with elevated peripheral renin activity, 15–70% of pediatric patients with arteriographically proven renal artery stenosis have normal peripheral plasma renin activity [7, 8]. Moreover, the false negative rate of intrarenal Doppler ultrasound in detecting renovascular hypertension in children is 48% [9]. Children with proven renovascular hypertension and normal Doppler ultrasounds are more likely to be cured by endovascular therapy or surgery [9]. In a recent study of children treated surgically for renovascular hypertension, 70% were cured and 26% showed improvement in blood pressure control [10].

Ganglioneuromas are rare, well-differentiated, usually benign tumors of neural crest origin. They tend to occur at a later age than their immature neuroblastoma counterparts (79 vs 16 months of age) and have a male to female ratio of 1.13:1 [1]. None of the children from the above three cited case series had a renal hilar ganglioneuroma [1, 4, 5]. One child did have partial stenosis of the renal artery from a retroperitoneal mass. Although the possibility of extrinsic compression of the renal vasculature is included in the differential diagnosis of renovascular hypertension, it is rarely noted in case series [8, 10, 11]. One of 54 children with renovascular hypertension from the series reported by Deal et al. from the Hospital for Sick Children had hypertension secondary to extrinsic compression by a tuberculous lymph node [11]. A series of six cases published in 1954 from Johns Hopkins included a child with a perihilar ganglioneuroma with cure of hypertension after removal of the kidney along with the surrounding mass [12].

We believe that our patient's hypertension was caused by a combination of renal ischemia due to blood vessel constriction by the mass, and the ensuing renal parenchymal insult. Both processes would induce hypertension by triggering the RAAC. Our case study demonstrates the shortcomings of ultrasonography as evidenced by both the report of an echogenic left kidney in light of a normal left kidney by the far more sensitive and specific imaging modalities of CT and MRI, and more dramatically, the failure of ultrasonography to detect the tumor. Despite the limitations of ultrasonography, which include variable operator expertise, one would expect to detect a 4-cm mass by this imaging modality. This particular scenario required further imaging studies to ascertain the etiology of the child's hypertension.

While neuroendocrine tumors are included in the vast differential diagnosis of pediatric hypertension, the underlying mechanism usually involves tumor hormone secretion. It is much less common for these tumors to cause hypertension by vascular compression. This child had a perinephric ganglioneuroma causing renovascular compromise, and consequent renal parenchymal ischemia. Unfortunately, the renal ultrasound was unable to detect the hilar mass, and it was not until an MRI was performed that the mass was discovered.

References

1. Geoerger B, Hero B, Harms D, Grebe J, Scheidhauer K, Berthold F (2001) Metabolic activity and clinical features of primary ganglioneuromas. Cancer 91:1905–1913
2. Ingelfinger JR (1993) Renovascular disease in children. Kidney Int 43:493–505
3. Ernst AA, Weiss SJ, Johnson WD, Takakuwa KM (1993) Blood pressure in acute vaso-occlusive crises of sickle cell disease. South Med J 6:590–592
4. Weinblatt M, Heisel M, Siegel S (1983) Hypertension in children with neurogenic tumors. Pediatrics 71:947–951
5. Lucas K, Gula M, Knisley AS, Virgi MA, Wollman M, Blatt J (1994) Catecholamine metabolites in ganglioneuroma. Med Pediatr Oncol 22:240–243
6. Nakano S, Kigoshi T, Uchida K, Morimoto S, Tsugawa R, Matsunou H (1996) Hypertension and unilateral renal ischemia (page kidney) due to compression of a retroperitoneal paraganglioma. Am J Nephrol 16:91–94
7. Dillon MJ (1997) The diagnosis of renovascular disease. Pediatr Nephrol 11:366–372
8. McTaggart SJ, Gelati S, Walker RG, Powell HR, Jones CL (2000) Evaluation and long-term outcome of pediatric renovascular hypertension. Pediatr Nephrol 14:1022–1029
9. Garel L, Dubois J, Robitaille P, Russo P, Filiatrault D, Grignon A, Dube J (1995) Renovascular hypertension in children: curability predicted with negative intrarenal Doppler ultrasound results. Radiology 195:401–405
10. O'Neill JA (1998) Long-term outcome with surgical treatment of renovascular hypertension. J Pediatr Surg 33:106–111
11. Deal JE, Snell MF, Barratt TM, Dillon MJ (1992) Renovascular disease in childhood. J Pediatr 121:378–384
12. Howard JE, Berthrong M, Gould DM, Yendt ER (1954) Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. Johns Hopkins Hospital Bull 94:51–85