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Severe Hypertension in an Adolescent Girl

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CASE PRESENTATION

Initial Presentation and History

A 14-year-old girl presented to the emergency department (ED) with pain and swelling in her right foot after a sledding accident. There was no history of head trauma, headaches, nausea, vomiting, vision changes, chest pain or palpitations, abdominal pain, peripheral edema, or sweating. Her initial examination revealed a blood pressure of 204/140 mm Hg, and several repeat blood pressure measurements showed similar results. She had a past history of a positive purified protein derivative test for tuberculosis and asthma, but no exacerbations had occurred during the last 5 years. There was no record of previous blood pressure measurements. She was not taking any prescribed or over-the-counter medications, did not smoke, and denied illicit drug use. Family history was negative for hypertension, end-stage renal disease, early atherosclerotic cardiovascular disease, obesity, diabetes, hyperlipidemia, or familial endocrinopathies.

Physical Examination

The patient was a well-developed, well-nourished adolescent. Her height was 5 ft 7.5 in (90th percentile for age), weight was 147 lb (90th percentile for age), pulse was 82 bpm, and respiratory rate was 20 breaths/min. Her body mass index was 22.7 kg/m². Extremity blood pressure measurements revealed the following: left arm, 204/127 mm Hg; right arm, 196/131 mm Hg; left leg, 169/118 mm Hg; and right leg, 197/124 mm Hg. Ophthalmologic examination was normal. Neck examination was negative for lymphadenopathy, thyromegaly, or bruit. Cardiac examination was normal and without murmurs; peripheral pulses were palpable, strong, and symmetric. Lungs were clear, and her abdominal examination was benign with no abdominal bruits. Dermatologic examination was unremarkable.

Key Point

Physical examination in an adolescent with hypertension should include a search for underlying causes of hypertension

such as heart murmurs (ie, cardiac diseases), femoral pulses (ie, coarctation of the aorta), palpable kidneys (ie, polycystic kidney disease), abdominal bruits (ie, renal artery stenosis), abdominal mass (ie, Wilms' tumor, neuroblastoma), café-au-lait spots (ie, neurofibromatosis), acanthosis nigricans (ie, insulin resistance, type 2 diabetes), malar rash (ie, systemic lupus erythematosus), retinal changes (ie, severe hypertension), thyromegaly (ie, hyperthyroidism), moon facies and truncal obesity (ie, Cushing syndrome), elfin facies (ie, Williams syndrome), and webbed neck and widely spaced nipples (ie, Turner syndrome).¹ Evidence of end-organ damage due to severe hypertension, such as left ventricular hypertrophy, acute cardiac failure, pulmonary edema, acute renal failure, eclampsia, or encephalopathy (presenting as strokes, seizures, or neurologic focal deficits), warrants emergency antihypertensive therapy.

Laboratory Studies

Results of laboratory studies performed in the ED are shown in **Table 1**. The patient was admitted to the pediatric intensive care unit (PICU) due to persistent severe hypertension. A constant infusion of labetalol reduced her blood pressure over the next 12 hours, and oral nifedipine was introduced. Results of laboratory tests obtained in the PICU are shown in **Table 2**.

HYPERTENSION IN CHILDREN

The prevalence of hypertension in the pediatric population is estimated at 1% to 3%, which is much lower than the 25% to 35% prevalence in adults.^{2,3} Hypertension in children is defined as average systolic or diastolic blood pressure greater than the 95th percentile for age, gender, and height.⁴ A diagnosis of hypertension is made only after confirming elevated blood pressure on 3 separate occasions; blood pressure must be measured using an appropriately sized blood pressure cuff after the

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Table 1. The Case Patient's Laboratory Values Obtained in the Emergency Department

Laboratory Test	Results	Normal Range
Sodium (mEq/L)	136	133–145
Potassium (mEq/L)	4.2	3.4–5.4
Chloride (mEq/L)	96	95–108
Bicarbonate (mEq/L)	23	22–28
Blood urea nitrogen (mg/dL)	13	6–22
Serum creatinine (mg/dL)	0.8	0.5–1.6
Calcium (mg/dL)	10.1	8.5–10.5
Cholesterol (mg/dL)	171	50–199
Renin (ng/mL/h)	8.57	1.31–3.95
Thyroid-stimulating hormone (μ IU/mL)	0.629	0.4–4.4
Human chorionic gonadotropin (mIU/mL)	< 1	0–5
Albumin (g/dL)	4.4	3.4–5.2
Hemoglobin (g/dL)	13.4	11.7–15.7
Leukocyte count ($\times 10^3/\mu$ L)	7300	3800–10,900
Platelet count ($\times 10^3/\mu$ L)	198	110–390
Urinalysis	Normal dipstick examination, negative microscopic analysis	
Renal ultrasound	Negative for hydronephrosis; both kidneys measured 10 cm in length (50th percentile for age)	

patient has been at rest for 5 minutes. The width of the blood pressure cuff should equal approximately two thirds the distance between the shoulder and elbow to avoid falsely elevated or depressed blood pressure readings.⁵ Measurement in the right arm is preferred to avoid missing a coarctation of the aorta. Blood pressure tables for children and adolescents based on gender, age, and height are available at www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm.

Screening

The Fourth Report of the National High Blood Pressure Education Program Working Group on Children and Adolescents⁴ recommends screening all children aged 3 years and older for elevated blood pressure with conventional sphygmomanometers and auscultation on a yearly basis. The report also recommends measuring blood pressure in children younger than 3 years if the child has a history of prematurity, very low birth weight, other neonatal complication requiring intensive care, congenital heart disease, recurrent urinary tract infections, hematuria, proteinuria, known renal disease or urologic malformations, family history of congenital renal

Table 2. The Case Patient's Laboratory Values Obtained in the Pediatric Intensive Care Unit

Laboratory Test	Results	Normal Range
C-reactive protein (mg/L)	1.2	0.05–5.00
ESR (mm/h)	6	0–20
Rheumatoid factor (IU/mL)	10	0–14
Antinuclear antibody	Negative	Negative
Anti-dsDNA antibody	Negative	Negative
Echocardiogram	Normal	
Tc 99m MAG3 renal scan		
Renal blood flow (time to peak, min)	Right kidney, 4.5; left kidney, 2.5	≤ 2.5
Differential function (%)	Right kidney, 60; left kidney, 40	50
MRA		
Abdominal aorta	Infrarenal aortic narrowing	N/A
Renal artery	Severe bilateral renal artery stenosis	N/A

ESR = erythrocyte sedimentation rate; MRA = magnetic resonance angiography; N/A = not applicable.

disease, solid-organ transplant, bone marrow transplant, treatment with medications that may increase blood pressure, systemic conditions associated with hypertension, and evidence of elevated intracranial pressure.⁴

Differential Diagnosis

Hypertension in children is often due to an identifiable underlying cause. In infants, hypertension is usually related to renal or vascular disease (Table 3). In children aged 12 years or younger, the majority of hypertension cases are related to renal diseases or coarctation of the aorta, but there are other less common causes of childhood hypertension (Table 3). In older children and adolescents (aged > 12 years), renal diseases continue to be the most common causes of hypertension, although essential hypertension should also be strongly considered. Secondary causes of hypertension in this older age-group are found much less frequently than in younger patients.⁵

Evaluation

The initial evaluation of hypertension and possible underlying causes of hypertension should include complete blood count; measurements of serum electrolyte, serum creatinine, blood urea nitrogen, calcium, cholesterol, uric acid, and renin levels; urinalysis; urine culture; and renal ultrasound.⁵

Table 3. Causes of Hypertension in Children

Age-Group	More Common Causes	Less Common Causes
Neonates and young infants	Renal artery thrombosis after umbilical-artery catheterization Coarctation of the aorta Congenital renal disease Renal artery stenosis	Bronchopulmonary dysplasia Patent ductus arteriosus Intraventricular hemorrhage
Children, 1 to 12 yrs	Renal disease, congenital and acquired Coarctation of the aorta	Renal artery stenosis Hypercalcemia Neurofibromatosis Neurogenic tumors Pheochromocytoma Mineralocorticoid excess (ie, primary hyperaldosteronism, 11 β -hydroxylase deficiency, 17 α -hydroxylase deficiency, apparent mineralocorticoid excess, Liddle syndrome, glucocorticoid remediable aldosteronism) Hyperthyroidism Transient hypertension after urologic and orthopaedic surgery Hypertension induced by immobilization (traction) Sleep apnea-associated hypertension Essential hypertension
Children > 12 yrs	Renal diseases, acquired Essential hypertension	Same as listed in children aged 1 to 12 yrs

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Key Point

The most common causes of hypertension in children are renal parenchymal diseases and renovascular etiologies. Renal parenchymal diseases include reflux nephropathy, obstructive uropathy, and both congenital and acquired renal diseases. Renovascular hypertension is often due to renal artery stenosis, with fibromuscular dysplasia being the most common cause of renovascular hypertension in the pediatric population.⁶ Primary (or “essential”) hypertension is a diagnosis of exclusion.

DIAGNOSIS OF THE CASE PATIENT

Our patient was diagnosed with hypertension (> 99th percentile for age) in the ED. Her initial work-up aimed at identifying possible renal diseases showed an increased peripheral plasma renin level and kidney sizes smaller than expected for a patient whose height and weight are at the 90th percentile for age. A Tc 99m MAG3 study, a nuclear imaging test to assess differential renal blood flow, showed significantly delayed uptake and excretion of technetium radionuclide by the right kidney compared with the left kidney. The significant differential in kidney perfusion provided sufficient evidence to suspect renovascular disease as the cause of our patient’s hypertension.

RENOVASCULAR HYPERTENSION

Renovascular hypertension, one of the common forms of identifiable hypertension, is defined as hypertension caused by renal ischemia, usually due to renal

artery stenosis. An elevated renin level strongly points to a renovascular etiology of hypertension. A decrease in renal perfusion activates the renin-angiotensin system, leading to release of renin and production of angiotensin II. Angiotensin II increases aldosterone release and causes sodium retention as well as increased renovascular resistance, ultimately resulting in renovascular hypertension. Clinical clues for the diagnosis of renovascular hypertension include the following: (1) onset of hypertension before age 30 years or after age 50 years, abrupt onset of hypertension, severe or resistant hypertension, symptoms of atherosclerotic disease elsewhere in the cardiovascular system, negative family history of hypertension, smoking, and unexplained congestive heart failure or acute pulmonary edema in the patient’s history; (2) abdominal and/or flank bruits on physical examination; and (3) laboratory findings demonstrating hypokalemia, alkalosis, hyponatremia, hyperreninemia, unexplained azotemia, angiotensin-converting enzyme (ACE) inhibitor-induced azotemia, and/or findings of a unilateral small kidney on renal imaging.⁷

Differential diagnoses of renovascular hypertension are listed in **Table 4**.⁸ The 2 most common causes of renal artery stenosis are atherosclerotic renal artery stenosis and fibromuscular dysplasia. Atherosclerosis accounts for 90% of renal artery stenosis, mainly affects patients aged 50 years or older, and usually involves the ostium and proximal third of the main renal artery and

Table 4. Causes of Renovascular Hypertension**Intrinsic lesions**

Atherosclerosis
 Fibromuscular dysplasia (ie, intimal,* medial, adventitial/periarterial)
 Aneurysm
 Emboli
 Arteritis (ie, polyarteritis nodosa, Takayasu's arteritis)
 Arteriovenous malformation or fistula
 Renal artery or aortic dissection
 Angioma
 Neurofibromatosis*
 Thrombus (ie, tumor, antiphospholipid syndrome)
 Rejection of renal transplant
 Renal artery injury (ie, thrombosis after umbilical artery catheterization,* surgical ligation, trauma, radiation, lithotripsy)
 Intrarenal cysts

Extrinsic lesions

Pheochromocytoma, paraganglioma
 Congenital fibrous band*
 Pressure from diaphragmatic crus*
 Tumors
 Subcapsular or perirenal hematoma
 Retroperitoneal fibrosis
 Ureteral obstruction
 Perirenal pseudocyst
 Stenosis of celiac axis with steal of renal blood flow

Adapted with permission from Kaplan NM. Kaplan's clinical hypertension. 8th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002:384.

*More common in children.

perirenal aorta.^{9,10} Fibromuscular dysplasia is a collection of vascular diseases whose pathologic classification is based on the involved arterial layer in which the lesions predominate (ie, intima, media, adventitia, or periarterial layer); it accounts for less than 10% of renal artery stenosis and tends to affect women aged 15 to 50 years.^{9,10} Other less common causes of renal artery stenosis in the pediatric population include large vessel arteritis, such as Takayasu's arteritis, Marfan's syndrome, and Ehlers-Danlos syndrome (associated with medial fibromuscular dysplasia).

Key Point

A severe elevation of blood pressure, regardless of the child's age, warrants aggressive evaluation aimed at identifying renal disease. For patients with persistent, severely elevated blood pressure (> 99th percentile for age, gender, and height), additional diagnostic tests are needed to rule out secondary causes of hypertension, such as echocardiogram, urine collection for catecholamines, measurement of plasma and urine steroid levels, and further imaging studies (eg, nuclear scan, computed

tomographic [CT] angiography, magnetic resonance angiography [MRA]), as indicated by clinical suspicion in an individual patient.

CONTINUED CLINICAL COURSE OF THE CASE PATIENT

Serologic studies of acute phase reactants were unremarkable. MRA of the abdomen showed severe narrowing of a 6-cm segment of the aorta below the renal arteries, with a 6-mm diameter lumen at the narrowest point, as well as significant bilateral proximal stenosis of the renal arteries (**Figure 1**). Reconstructive surgery was performed to replace the lower aorta and renal arteries with a vascular graft. Pathologic testing of the native aorta and renal arteries revealed acute and chronic panarteritis with inflammatory involvement of the tunica adventitia, media, and intima. There was also intimal hyperplasia resulting in severe reduction of the luminal diameter (**Figure 2**). These findings (ie, panarteritis, aortic narrowing, intimal hyperplasia) were strongly suggestive of Takayasu's arteritis.

TAKAYASU'S ARTERITIS

Takayasu's arteritis, also known as "pulseless disease," is a rare condition involving the large elastic arteries, primarily the aorta and its major branches. It mainly affects young girls and women (9 times more often than men) in their second and third decades of life, with peak age of onset of 15 to 20 years.¹¹ Takayasu's arteritis is most commonly seen in Japan, Southeast Asia, India, and Mexico. In North America, the estimated annual incidence is 2.6 cases per 100,000 people.¹² In Japan, the most common sites of involvement are the aortic arch and its major branches, whereas in India the most common sites are the thoracic aorta distal to the aortic arch and the abdominal aorta with its major branches.¹³

Pathophysiology

Takayasu's arteritis is characterized by panarteritis with a mononuclear infiltrate penetrating the layers of the arterial wall. The acute vasculitic phase is characterized by transmural inflammation of elastic arteries with lymphocytes, monocytes, neutrophils, and occasionally multinucleated giant cells. The chronic phase is characterized by intimal fibrosis and scarring of the tunica media, eventually resulting in luminal narrowing and occlusion.¹¹ Cellular immune responses involving T cells, antigen-presenting cells, and macrophages are basic elements in Takayasu's arteritis; no autoantibody is implicated in the pathogenesis.¹⁴ The mechanisms of injury in Takayasu's arteritis are derived from pathogenic models in giant cell (temporal) arteritis. This is a T-cell-dependent process involving activation of immature dendritic cells located in the tunica adventitia of



Figure 1. Magnetic resonance angiogram showing proximal stenosis of renal arteries and severe narrowing of aorta below renal vessels.

arteries, which results in cytokine secretion and in turn activates monocytes and macrophages, causing systemic inflammation.¹⁴ Vascular inflammation leads to wall thickening, fibrosis, stenosis, and thrombus formation.

Clinical Manifestations

Clinical manifestations of Takayasu's arteritis reflect end-organ ischemia and range from asymptomatic patients with abdominal bruits or nonpalpable pulses to catastrophic neurologic impairment. Most patients have vascular bruits (often multiple) and diminished or absent pulses.^{15,16} Systolic blood pressure differences greater than 10 mm Hg between the right and left arms are due to subclavian stenosis. When cerebral arteries are involved, patients can present with stroke, postural dizziness, seizures, and amaurosis. Renal involvement is seen in 28% to 75% of Takayasu's arteritis patients; it often presents as hypertension caused by renal artery stenosis with preservation of renal function.^{12,15,17,18} With pulmonary involvement (14%–100% of patients), patients may have cough, dyspnea, chest pain, and/or pulmonary hypertension.¹⁹ Takayasu's retinopathy occurs in up to 37% of patients.¹⁷ Congestive heart failure, aortic regurgitation, and dilated cardiomyopathy reflect involvement of the coronary arteries. Vascular disease in Takayasu's arteritis is accompanied by fever, malaise, arthralgias, myalgias, weight loss, and anemia.

Diagnosis

Angiography is the gold standard for diagnosis of renovascular disease but is performed only when surgical or invasive radiologic procedures are considered for

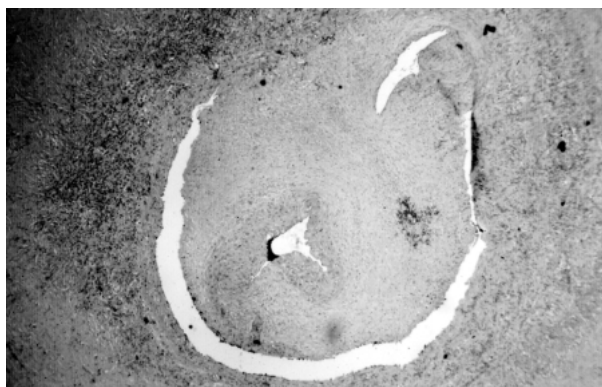


Figure 2. Photomicrograph of a section of renal artery revealing intimal and medial collagenous thickening and chronic inflammation. The vessel lumen is markedly reduced.

anatomic correction. Histologic diagnosis is limited to patients undergoing a revascularization process. Spiral CT angiography or MRA are the imaging modalities of choice. Spiral CT angiography is superior to MRA in detecting accessory renal arteries and abnormalities in the distal area of the renal arteries. However, spiral CT angiography requires a higher radiation dose and larger volume of contrast than MRA and thus has a higher risk of nephrotoxicity. Therefore, MRA is preferred over spiral CT angiography to diagnose Takayasu's arteritis.²⁰ MRA and spiral CT angiography are useful, but they may not be sensitive enough to detect arterial wall abnormalities. Positron emission tomography with F-fluorodeoxyglucose has a high sensitivity for detecting metabolic changes in the arterial wall but is expensive.²¹

At times, it may be difficult to distinguish fibromuscular dysplasia from Takayasu's arteritis without histologic evidence because their appearance on angiographic examination may be similar, especially in intimal fibromuscular dysplasia of the multivessel type.¹⁰ Large-vessel vasculitis may occur in the absence of changes in acute phase reactants in up to 40% of cases.²²

Treatment

Indications for surgery include hypertension with severe renal artery stenosis, extremity claudication limiting activities of daily living, cerebrovascular ischemia or severe stenosis in 3 or more cerebral vessels, moderate aortic regurgitation, or cardiac ischemia with confirmed coronary artery involvement.¹⁸ Treatment for active Takayasu's arteritis includes glucocorticoids (to which 50% respond)²³ and methotrexate (to which a further 25% respond).²⁴ Management of hypertension with ACE inhibitors and prevention and treatment of thrombosis are important issues to consider when managing patients with Takayasu's arteritis.

FOLLOW-UP OF THE CASE PATIENT

Our patient underwent aortic interposition graft and bilateral renal artery bypass 1 month after her initial presentation. She became normotensive for 16 weeks after surgery without taking antihypertensive medication and was then lost to follow-up. About a year later, the patient returned with hypertension. Repeat MRA showed recurrent aortic stenosis in the upper margin of the graft. The patient underwent balloon dilatation and bilateral renal artery stent placement. The patient's hypertension resolved but gradually recurred over the next 7 months. Follow-up MRA revealed occlusion of the right renal artery with moderate stenosis of the left renal artery. The patient was placed on lisinopril and has maintained good blood pressure control. She has chronic kidney disease with a serum creatinine level of 1.2 mg/dL (calculated glomerular filtration rate, 79 mL/min per 1.73 m²) and needs close monitoring for blood pressure control, observation of the progression of her renal disease, and reduction of cardiovascular risk factors.

The case patient was not treated with immunosuppressants for her Takayasu's arteritis for several reasons: the markers for inflammation were negative, there was no clear indication for anti-inflammatory treatment, and immunosuppressants could potentially reactivate her tuberculosis (given her history of a positive purified protein derivative). It was decided that the best course of action was to follow the patient closely, control her blood pressure with an ACE inhibitor, and monitor her disease progression with imaging studies and renal function tests.

CONCLUSION

Takayasu's arteritis is one of several potential underlying diseases in children with renovascular hypertension. This case demonstrates the importance of a logically directed investigation into the differential diagnosis of hypertension in children. Persistent severe elevations of blood pressure in children warrants aggressive evaluation to identify renal causes of hypertension. Primary or essential hypertension is a diagnosis of exclusion. Once identified, correcting the underlying cause of hypertension in a child can improve or normalize blood pressure, thus avoiding lifelong pharmacologic antihypertensive treatment. **HP**

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