Journal of Primary Care & Community Health
1–5

DOI: 10.1177/2150132719843437
journals.sagepub.com/home/jpc
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The Evaluation of a 19-Year-Old With Hypertension and Proteinuria: A Case Report

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Abstract

A 19-year-old male presented to the clinic and was found to be prehypertensive and have proteinuria on urine testing. He was subsequently diagnosed with focal segmental glomerulosclerosis (FSGS). Initial workup for pediatric hypertension includes urinalysis, chemistry panel, lipid panel, and renal ultrasound. Abnormalities on urinalysis, including proteinuria, hypercholesterolemia, and low serum albumin in children are characteristic of nephrotic disease. FSGS is a type of kidney pathology that often contributes to nephrotic disease and results from a variety of causes. For the primary care provider, being aware of the guidelines for pediatric hypertension screening and evaluation is important as 20% of children with hypertensive disease are due to kidney disease. FSGS is the third leading cause of end-stage renal disease in children aged 12 to 19 years, and its incidence was found to be rising in a study of Olmsted County, MN residents. Treatment to complete or partial remission of the proteinuria can slow the progression of renal disease. In this case report, we will discuss the evaluation of pediatric hypertension workup with proteinuria, specifically due to FSGS, and review current management strategies.

Keywords

children, disease management, primary care, health outcomes, patient-centeredness

Case Presentation

Our patient was a 19-year-old male who presented for a general medical exam and blood pressure check prior to leaving for college. He was overall healthy and active. He noted high blood pressure readings at home but did not remember specific details. He also reported occasional frothy urine. He noted no other symptoms. He denied alcohol, tobacco, and drug use. He was taking a multivitamin and fish oil as well as occasional acetaminophen. He had a family history of hereditary nephritis in his mother that resulted in 2 kidney transplants, the first at age 30 years. His paternal grandfather had the same disease. He did have urine testing at age 4 that was normal without signs of hereditary nephritis. During a routine visit at age 13, he had a blood pressure reading of 140/88 mm Hg, which was greater than the 95th percentile for height and age. At that visit, he had screening labs with a fasting blood sugar of 93 mg/dL, creatinine of 0.7 mg/dL, and a normal urine dipstick.

On his physical exam, his blood pressure was 130/88 mm Hg and pulse was 59. His body mass index was 26.9 kg/m^2. He was a well appearing young adult. His cardiovascular exam was normal without murmurs and his respiratory exam was benign. His neurologic exam was normal. He had no edema, skin rashes, or musculoskeletal abnormalities noted.

Because of the patient's history of elevated blood pressures and family history of kidney disease, we obtained basic labs, including a thyroid-stimulating hormone (TSH), creatinine, sodium, potassium, and urinalysis. TSH and electrolytes were normal. His creatinine was 1.3 mg/dL (range 0.6-1.3 mg/dL). His urinalysis showed protein of 237 mg/dL, trace hemoglobin, and fatty casts. He returned for further discussion and repeat urinalysis, which again showed proteinuria. An in-depth history was obtained that was unrevealing for a cause of his proteinuria with the exception of his family history. He underwent a 24-hour urine collection that showed 7 g of protein. His liver enzymes were within normal limits. He subsequently was evaluated by Nephrology who performed additional testing,

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including coagulation studies that were normal and a kidney biopsy. His kidney biopsy showed focal segmental glomerulosclerosis (FSGS) with moderate chronic changes including focal global glomerulosclerosis and moderate tubulointerstitial scarring. He was diagnosed with FSGS thought to be hereditary. Given his strong family history of kidney disease, he visited with Medical Genetics and is in the process of undergoing genetic testing.

Discussion

Screening for hypertension in pediatric patients differs from screening for adults. The American Academy of Pediatrics (AAP) recommends annual screening for children older than 3 years, and more frequently for patients with obesity, renal or heart disease, or who are taking medications that could raise blood pressure.[1] However, the United States Preventive Services Task Force (USPSTF) has concluded that there is insufficient evidence (I recommendation) to recommend routine blood pressure screening in asymptomatic children and adolescents.[2] The American Academy of Family Physicians (AAFP) has issued an "Affirmation of Value" supporting the AAP's guidelines while withholding a full endorsement.[3] Diagnosis of pediatric hypertension uses different criteria than adults, stratifying readings into percentiles for patient age, sex, and height. A systolic or diastolic blood pressure blood pressure greater than the 95th percentile is considered elevated. If it is greater than the 95th percentile on more than 3 occasions, this is indicative of hypertension.[1] Once the diagnosis of pediatric hypertension has been established, careful history and physical exam must be performed to determine primary or secondary causes. Nearly 20% of hypertension in pediatric patients is due to kidney disease. Patients with kidney disease are more likely to develop hypertension or hypertension could be the presenting symptom.[1]

The AAP recommendations for the initial workup of pediatric hypertension include a urinalysis, chemistry panel, lipid profile, and a renal ultrasound if the child is younger than 6 years or with abnormal UA or renal function. Additional testing may be indicated based on the history or exam. Some of these additional tests include a compliment level, antinuclear antibody, and possibly hepatitis B and C or HIV testing in high-risk populations.[1]

Urinalysis with a dipstick is an initial screening test that can guide further workup. Protein excretion on urine dipstick should not be detected. In children, proteinuria can be due to multiple factors including fevers, dehydration, and stress. This can be transient or can be complicated further by orthostatic proteinuria. Orthostatic proteinuria is a benign condition in which there is normal protein excretion when a child is recumbent but increased excretion when in an upright position. Abnormalities on the initial urine dipstick should be followed up with repeat testing, and if persistently positive should be followed up with quantitative testing. Quantitative testing includes a spot urine protein/creatinine ratio or a 24-hour urine protein. The 24-hour urine collection can be logistically challenging in pediatric patients. A urine protein/creatinine ratio with a first-morning-void can rule out orthostatic proteinuria as a cause of the abnormal urinalysis. An abnormal urine protein/creatinine ratio is >0.2.

The workup for persistent proteinuria is similar to the workup of hypertension as described above with the addition of albumin, C3 and other testing depending on the patient risk factors. A kidney biopsy is recommended for children aged 12 years and older. Nephrotic syndrome in children is defined as proteinuria of >1 g of protein per square meter of body surface area per day.[4] Other features in childhood nephrotic syndrome include low serum albumin (<2.5 g/dL) and hypercholesterolemia (total cholesterol >200 mg/dL).[5] In adults, proteinuria of 3.5 g or more in a day is defined as nephrotic range proteinuria. Our patient had an estimate of 7 g in a day, classifying him in the nephrotic range. There were also fatty casts present in his urine. Fat bodies and hyaline casts can also be present on a urinalysis, though red cells are uncommon.

Nephrotic syndrome (NS) can have different etiologies. The most common cause of NS in children is minimal change disease, which is characterized by effacement of podocytes and is often treated without a kidney biopsy in young children. Other causes include FSGS, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy, lupus, and amyloidosis. Classification of nephrotic disease is done with kidney biopsy. The defining feature of FSGS is a disease process that affects some glomeruli while sparing others, as well as affecting only certain segments of a glomerulus, as opposed to global glomerulonephropathy. The portion of the glomerulus that is typically affected in FSGS is the podocyte, specifically in primary disease. This damage can be primary in nature or secondary to other causes, for example systemic or circulating factors that cause damage.[6]

The incidence of glomerular disease, specifically FSGS, was found to be rising in a study of Olmsted County, MN residents.[7] It affects about 35% of adults with nephrotic disease. FSGS is further classified as primary, secondary and genetic. Secondary causes of FSGS include viral infections like HIV, hepatitis C, or parvovirus B19 and may also be due to drugs such as heroin, interferon, bisphosphonates, and anabolic steroids. Morbid obesity, autoimmune disease such as lupus, or vasculitis can also be causes of secondary FSGS.

FSGS may result from genetic mutations of which at least 20 have been identified.[8] In general, these gene mutations affect the podocyte function of the glomerulus. While most of these mutations result in renal disease, a few have been associated with extrarenal manifestations including Denysh-Drash syndrome, Frasier syndrome, and nail-patella syndrome. FSGS with an autosomal recessive etiology typically presents in childhood whereas autosomal

dominant FSGS typically presents in adulthood.[9] Moreover, pediatric patients with genetic etiologies of FSGS are more likely to present clinically with nephrotic syndrome than adult inherited forms. Phenotypic expression, especially in adult forms, may vary significantly and penetrance is thought to depend, in part, on the interactions of gene expression and environmental factors.[8] Despite important advances in understanding the genetic components of FSGS, there are many factors that play a role and additional research needs to be done to understand the complex pathogenesis of podocyte injury.

Identifying familial forms of FSGS is important due to the effect on both treatment as well as consideration of genetic counseling. For example, steroid therapy, a mainstay in the management of NS, is much more likely to fail when NS occurs from FSGS with a genetic etiology, especially in children.[8] However, genetic testing is currently expensive, time consuming, and therefore is not routinely done. Although upcoming next-generation sequencing may reduce costs, current testing focuses on specific genetic mutations when suspicion warrants testing. Major clues to genetic forms of FSGS include congenital onset of nephrotic syndrome, lack of steroid responsiveness to therapy, consanguineous (ie, genetically related) parents, syndromic manifestations and positive family history.[9]

Treatment of children and adolescents with FSGS should be in consultation with a pediatric nephrologist. The goal of treatment in NS from FSGS is achieving remission or resolution of the proteinuria and, if not possible, then preservation of kidney function. A urine protein/creatinine ratio of <0.2 or a urine dip protein $<+1$ for 3 days indicates remission. Relapsing nephrotic range proteinuria can occasionally occur after achieving remission. NS is often classified as frequently relapsing, steroid-dependent, or steroid-resistant, depending on the clinical course.

The Kidney Disease: Improving Global Outcomes Glomerulonephritis Workgroup (KDIGO)[10] recommends initial treatment of NS with corticosteroids for 12 weeks for the presenting episode. The initial dose of prednisone in childhood NS is 2 mg/kg/d with a maximum of 60 mg once daily. This dose is used for 4 to 6 weeks and then reduced to a dose of 1.5 mg/kg/d every other day for 2 to 5 months with a tapering plan thereafter. This duration of treatment showed a reduction in risk of relapse when compared with an 8-week course. The starting steroid dose for treating a relapse is the same as for the initial episode, and should be given until remission for 3 days. The dose should again be decreased to 1.5 mg/kg on alternating days for at least 4 weeks. Subsequent relapses should be treated similarly. The Children's Nephrotic Syndrome Consensus Conference support these treatment guidelines for steroid-sensitive, steroid-dependent, and relapsing nephrotic syndrome.[11] Treatment to partial or complete remission of the proteinuria can slow the progression of renal disease.[12]

Treatment of steroid resistant forms of FSGS is more challenging and requires a more tailored approach. Calcineurin inhibitors such as tacrolimus and cyclosporine have been shown to benefit patients with complete or partial remission.[13] These treatments should be used for a minimum of 6 months. A study comparing cyclosporine and mycophenolate/dexamethasone combination showed that they were similar in effect, though the complete or partial remission rates were 46% and 33%, respectively.[14] The KDIGO Workgroup recommends against using cyclophosphamide or rituximab.[15]

There are other considerations for treatment of FSGS. Additional therapy for NS includes treating hypertension and providing renal protection with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). A meta-analysis that examined the treatment of non-diabetic renal disease, including glomerular disease, showed that ACE inhibitors decreased blood pressure and decreased proteinuria and thus slowed progression of the kidney disease.[16] A low-fat diet (fat $<30\%$ of caloric intake) can help with dyslipidemia and prevent atherosclerosis. Dietary protein intake should remain in the range of 0.8 to 1 g/kg daily. Obese patients should be encouraged to lose weight. Nephrotic syndrome also increases the risk of infections in children due to the nature of the disease as well as the immunosuppressive treatment. Children with FSGS should be immunized with the special attention to the both the 13- and 23-valent pneumococcal vaccines. They should also receive an annual inactivated influenza vaccine. However, it is recommended to defer live vaccination if the patient is on a dose of steroids of 2 mg/kg/d. Thromboembolism is a potential complication of nephrotic syndrome, though treatment with anticoagulation is not recommended unless symptoms of an embolism develop.

One of the most significant complications of FSGS is the possibility of renal failure. FSGS is the third leading cause of end-stage renal disease in children between the ages of 12 and 19 years, behind glomerulonephritis and cystic and hereditary conditions. End-stage renal disease would require renal replacement with hemodialysis or kidney transplantation. Children with end-stage renal disease tend to have better outcomes than adults.[17]

Our 19-year-old male was ultimately treated with lifestyle interventions and conservative therapy. He was placed on a low-protein diet of 0.8 to 1 g/kg/d of protein, low-salt diet of less than 4 g, and recommendations to avoid nephrotoxic agents such as nonsteroidal anti-inflammatory drugs. For blood pressure control, he was started on losartan 50 mg daily with a goal of systolic blood pressure less than 120 mm Hg. He returned to the clinic 1 year later and had mildly improved proteinuria of 5.5 g/24 h and stable creatinine at 1.39 mg/dL. He is undergoing genetic testing due to his familial kidney disease.

Conclusion

Primary care providers play an important role in screening for pediatric diseases, including pediatric hypertension and nephrotic disease. Blood pressure screening for children should be done annually starting at age 3 years and more often if the patient has risk factors for elevated blood pressure. Interpretation of pediatric blood pressure should be based on normal ranges for age, gender, and height. If blood pressure is considered elevated on 3 readings, the patient should have a workup for hypertension with labs and a urinalysis. Abnormalities on this workup should be pursued accordingly.

If proteinuria is identified on urinalysis, it should be repeated. If persistently elevated, it should be evaluated for potential nephrotic syndrome. The evaluation of nephrotic range proteinuria often involves kidney biopsy. While minimal change disease is the leading cause of nephrotic syndrome in children, FSGS is also a common and increasing cause of nephrotic syndrome.

Treatment of FSGS should be undertaken in consultation with a pediatric or adult nephrologist and typically involves immunosuppression with steroids and/or calcineurin inhibitors. Although less common, genetic-mediated etiologies of FSGS are less responsive to steroid therapy and thus require other immunosuppressant therapies. Primary care providers should be aware of the adjunctive treatment for these patients as well, including diet and blood pressure control, ensure adequate immunization, as well as monitor for potential complications of thromboembolism and infection.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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