PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on the "Evaluation of Proteinuria." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Evaluation of Proteinuria:

Developed by Peter Gill and Dr. Verna Yiu for Pedscases.com.
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This podcast was written by Peter Gill and Dr. Verna Yiu. Peter is a medical student at the University of Alberta. Dr. Yiu is a pediatric nephrologist at the Stollery Children's Hospital in Edmonton, Alberta, Canada.

Preamble

You are completing a pediatric emergency shift and just finishing assessing a 2 year old with vomiting and diarrhea. You get the initial results back from the urinalysis and it reveals 1+ proteinuria. What does that mean? What do you need to do with that information?

Introduction

This podcast addresses the evaluation of proteinuria in children. Proteinuria is a well-documented and common finding on urinalysis in children in both doctor's offices and emergency rooms. Most cases are transient or benign. At least 10% of children will have proteinuria at some time in excess of 20-30 mg/dl (or 1+ on dipstick), which decreases to 0.5% for 3 consecutive samples. There is also a rise in prevalence from preteen to adolescence with males lagging 3 years behind. Some authors suggest that proteinuria is increased in females. In the first part of this podcast, we will help you develop an approach to the evaluation of proteinuria. We will then go through a brief overview of some of the common causes of proteinuria in children.

Definition

To start - what is proteinuria? Proteinuria is defined as greater than normal amounts of protein in the urine. But how much is too much?

In adults, proteinuria is defined as greater than 150 mg/day of protein in the urine. However, in pediatrics it tends to vary with age and body surface area. In children, proteinuria is defined as greater than 100 mg per meter squared per day, but in neonates it is greater than 300 mg per meter squared per day.

Well shouldn't there be no protein in the urine at all? Actually, there is a normal rate of protein excretion per day and this can vary with activity. Normal urine is composed of 40% Tamm-Horsfall protein, 40% albumin, 15% Immunoproteins and 5% other plasma proteins.

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Causes of Proteinuria

Often times the clinical picture will lead you to the likely cause of proteinuria. The key evaluation tool is to determine if the proteinuria is transient or persistent. The following are common cause of proteinuria in children.

Orthostatic proteinuria

Around 60 percent of all cases of proteinuria are due to orthostatic proteinuria, especially in adolescents. If initial investigations are normal, an orthostatic test can be completed. Ask the patient to empty their bladder before going to bed, lie flat all night in bed, and then urinate first thing in the morning after getting up. Additional urine samples are then collected throughout the day with a final urine sample prior to bed. A diagnosis is confirmed if the morning sample is protein-free but the evening sample contains protein. In general, kids with orthostatic proteinuria should have under 1 gram of protein in full 24 hours.

Transient Proteinuria

Nearly half of all cases of proteinuria in children are transient and resolve spontaneously. Transient proteinuria can be due to febrile illnesses, seizures, strenuous exercise, emotional stress, serious illness like congestive heart failure and abdominal surgery. In these circumstances, if another etiology is suspected, a detailed work-up is not needed.

Glomerular

Proteinuria due to glomerular pathology is usually persistent and is less likely to be a benign cause. Proteinuria can be secondary to glomerular diseases such as acute glomerulanephritis, lupus nephritis and Focal Segmental GlomeruloSclerosis. The history, physical examination, investigations and complete urinalysis will assist to differentiate between the various etiologies. If proteinuria is over 40 mg per meter squared per hour, or over 3 grams in a 24 hour period, it is termed heavy or nephrotic range proteinuria. The most common cause of nephrotic syndrome in children is minimal change disease.

Tubulointerstitial

Proteinuria due to tubulointerstitial pathology is also usually persistent. Causes include interstitial nephritis, acute tubular necrosis and cystitis. Proteinuria of tubulointerstitial disease is generally mild.

Structural Abnormalities

Finally, structural abnormalities should be considered with proteinuria. This includes reflux nephropathy, renal hypoplasia or dysplasia, polycystic kidney disease or hydronephrosis.

Pathophysiology

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When approaching renal problems in particular, they are best understood by breaking then down into simple principles. In general, there are three pathophysiologic mechanisms by which proteinuria can occur: leaky filter units or glomeruli, inadequate reabsorption by the kidney tubules, or too much protein in the blood. Therefore, the first cause of proteinuria is due to a defect in the glomerular selective permeability leading to increased filtered proteins. For example, this is the mechanism of nephrotic syndrome.
Secondly, it can be due to inadequate tubular protein reabsorption and is an indication of tubulointerstitial disease. This is the mechanism of Acute Tubular Necrosis, or ATN.
The third mechanism is due to elevated concentration of normal or abnormal levels of plasma proteins. This occurs in an adult disease called multiple myeloma with an extremely high concentration of immunoglobulins.

History

Evaluation of proteinuria consists of a thorough history and physical examination. The history will focus on any associated symptoms and a review of systems. Make sure to inquire about any recent infections. Ask if there is a history of skin rash, abdominal pain, bloody diarrhea and joint pains to look for evidence of lupus, or systemic lupus erythematosus (SLE). Asking about specific urinary tract symptoms such as fever, dysuria, urinary frequency, gross hematuria or suprapubic pain is important to rule out UTI. Attempt to determine if there is a history of vigorous exercise, bruising or recent injuries. If the patient is a female and depending on age, ask about menses. Ask about a family history of collagen vascular diseases like lupus, renal transplant or dialysis, kidney stones, or polycystic kidney disease. Obtain a medication history, particularly if the pt has started any new medications.

Physical Exam

Your physical examination will focus on the key aspects of renal assessment. Accurate height, weight and blood pressure are essential. Assess the patients' fluid status and look for evidence of edema in the peripheral extremities or ascites. An abdominal exam will look for evidence of a palpable kidney. The physical examination will also look for other signs of skin and joint involvement. Do not forget to examine the genitalia for scrotal or labial edema.

Investigations

The key is to quantitate proteinuria and determine how much protein there is in the urine. The universal method to analyze urine is the random spot urine qualitative colorimetric test strips, i.e. the urinalysis or "dipstick" These strips give a crude estimate of the amount of protein. The dipstick is most sensitive to albumin and poorly quantifies other types of protein. Trace proteinuria indicates approximately 15 mg/dl, 1+ indicates 20-30 mg/dl, 2+ is 100 mg/dL, 3+ is 300 mg/dL and 4+ is greater than 2000 mg/dL.

However, it is good to be aware of situations that may give a false positive result. These include alkaline urine, highly concentrated urine, gross hematuria, pyuria, bactiuria and ammonia compounds. False Negatives may occur if there is very dilute urine or acidic urine.

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A more accurate assessment of proteinuria is the spot urine protein/creatinine ratio which correlates well with 24 hr. protein excretion. Normally, a child under the age of 3 will have under < 10 mg protein/mmol of creatinine and a child under the age of 10 will have under 7 mg protein/mmol of creatinine.

However, the gold standard is a 24 hour timed urine collection. This is the ideal method to quantify, especially if you are concerned that there is a large amount of protein. Nephrotic range proteinuria is greater than 40 mg per meter squared per hour. This may not be practical in a non-toilet trained toddler so a good urine protein/creatinine ratio would be a good alternative.

Approach to Investigation and Management

When assessing proteinuria in afebrile child, the first step is to repeat the urinalysis when the child is afebrile. If the dipstick remains positive despite absence of any stressors at >1+, then the child needs further evaluation as below. If repeat urinalysis is negative for protein, then it is a transient cause and no other tests need to be done.

Once you are sure that the cause of proteinuria is persistent and not transient, the next most common diagnosis when the history and physical are unremarkable is orthostatic proteinuria. In order to prove this diagnosis, you need to show the presence of proteinuria at a time of activity (that is, daytime) and absence of proteinuria when recumbent (i.e. right upon waking up). The easiest thing to do is to send the patient to collect 2 random urine samples and have them bring to the lab for urine protein/creatinine ratio: one first thing in the morning within 30 minutes of getting up and then another sample anytime in the afternoon. Make sure it is labeled accurately
with the time. Otherwise, you won't be able to tell if it is a postural cause. The degree of proteinuria that you can get with orthostatic in the daytime can be quite high but the analysis will always be negative in the morning. If you get these results, then you have made the diagnosis and no further follow-up is necessary.

Further evaluation is indicated if there are no postural changes with proteinuria, if there is persistent proteinuria on repeated samples and lastly, if there is co-existent hematuria and/or any systemic symptoms. This includes looking for evidence of underlying etiology such as glomerulonephritis. Lab work to order would include CBC, electrolytes, creatinine, blood urea nitrogen, cholesterol, albumin, serum complement C3/C4 and ANA. Quantification of the exact degree of protein with a 24 hour protein collection may be useful at this time.At this point in time, it would be prudent to consult a pediatric nephrologist for further assessment and consideration of renal biopsy and appropriate therapy.

When to refer?

You may come to a point at which you are out of your league and further assessment is required by a pediatric nephrologist. Some reasons to refer are:

1) Documented presence of hematuria and proteinuria and/or persistent proteinuria.

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2) Nephrotic range proteinuria.

3) Nephritic symptomatology.

4) Signs of systemic disease such as joint pains, rash, etc. and suspect CT disease.

5) Association with impaired renal function, and/or hypertension.

6) Parental anxiety.

Summary

In summary, proteinuria is a very common laboratory finding in pediatric patients. Common being common, it is generally benign - either transient or orthostatic. It is always important to take a complete history and do a thorough physical exam because the other possibilities are serious conditions that need to be diagnosed early and potentially treated. A good take home message is that presence of hematuria along with proteinuria is a bad sign and indicates significant parenchymal renal disease. If there is blood AND protein in the urine, this is not benign and needs further assessment and testing. Never be shy about contacting a pediatric nephrologist if you ever have concerns of a patient with proteinuria. Further investigations that a subspecialist may do include imaging studies and renal biopsies as indicated.

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